PCT/EP2004/050082

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I also certify that the application is now proceeding in the name as identified herein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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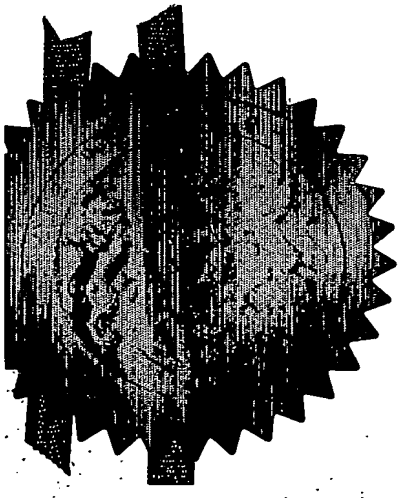

Signed Andrew Gerry

Dated 25 May 2004

GB 0310986.5

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of:

PLIVA-ISTRAZIVACKI INSTITUT D.O.O.,
Prilaz baruna Filipovica 29,
10000, ZAGREB,
Croatia

Incorporated in Croatia,

[ADP No. 08855231001]

Patents Form 1/77

Patents Act 1977
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13 MAY 2003
LONDON

The Patent Office

1/77

14MAY03 E806935-6 D02029
P01/7700 0.00-0310986.5

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — ARG/DAB/PB60261P

2. Patent application number
(The Patent Office will fill in his part) — 0310986.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

6935706003

United Kingdom
see continuation sheet for further applicant(s)

SECTION 6(3) 1977 ACT) APPLICATION FILED 30/4/04

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Patents ADP number *(if you know it)*

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	1
Description	49
Claim(s)	7
Abstract	1 only
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10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature _____ Date 13-May-03

A R Gladwin

12. Name and daytime telephone number of person to contact in the United Kingdom

A R Gladwin 01438 762051

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a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
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c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
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CONTINUATION SHEET

Reference: ARG/DAB/PB60261P

Further Applicant (s)
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Ulica grada Vukovara 49, Zagreb, Croatia

Country of incorporation: Croatia

8004673001

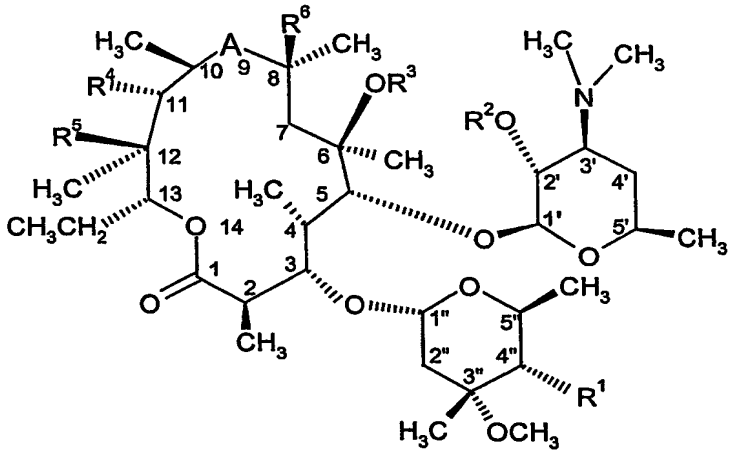
NOVEL COMPOUNDS

The present invention relates to novel semi-synthetic macrolides having antimicrobial activity, in particular antibacterial activity. More particularly, the invention relates to 14- and 15-membered macrolides substituted at the 4" position, to processes for their preparation, to compositions containing them and to their use in medicine.

Macrolide antibacterial agents are known to be useful in the treatment or prevention of bacterial infections. However, the emergence of macrolide-resistant bacterial strains has resulted in the need to develop new macrolide compounds. For example, EP 0 895 999 describes derivatives modified at the 4" position of the macrolide ring having antibacterial activity.

According to the present invention, we have now found novel 14- and 15-membered macrolides substituted at the 4" position which also have antimicrobial activity.

Thus, the present invention provides compounds of general formula (I)



(I)

wherein

A is a bivalent radical selected from -C(O)-, -C(O)NH-, -NHC(O)-, -N(R^7)-CH_2-, -CH_2-N(R^7)-, -CH(NR^8R^9)- and -C(=NR^{10})-;

R^1 is -$O(CH_2)_dXR^{11}$;

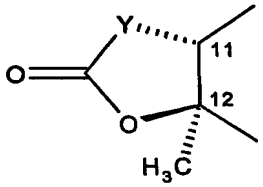
R^2 is hydrogen or a hydroxyl protecting group;

R^3 is hydrogen, C_{1-4}alkyl, or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R^4 is hydroxy, C_{3-6}alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl, or C_{1-6}alkoxy optionally substituted by C_{1-6}alkoxy or -$O(CH_2)_eNR^7R^{12}$,

R^5 is hydroxy, or

R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:



wherein Y is a bivalent radical selected from $-CH_2-$, -CH(CN)-, -O-, $-N(R^{13})-$ and $-CH(SR^{13})-$;

R^6 is hydrogen or fluorine;

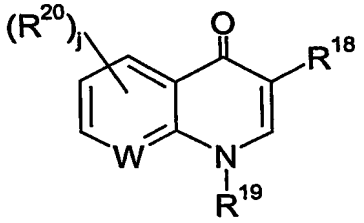
R^7 is hydrogen or C_{1-6}alkyl;

R^8 and R^9 are each independently hydrogen, C_{1-6}alkyl, $-C(=NR^{10})NR^{14}R^{15}$ or $-C(O)R^{14}$, or

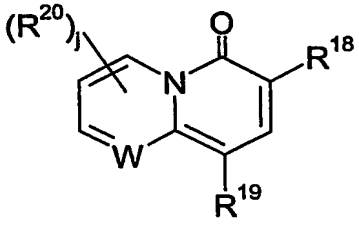
R^8 and R^9 together form $=CH(CR^{14}R^{15})_f$aryl, $=CH(CR^{14}R^{15})_f$heterocyclyl, $=CR^{14}R^{15}$ or $=C(R^{14})C(O)OR^{14}$, wherein the alkyl, aryl and heterocyclyl groups are optionally substituted by up to three groups independently selected from R^{16};

R^{10} is $-OR^{17}$, C_{1-6}alkyl, $-(CH_2)_g$aryl, $-(CH_2)_g$heterocyclyl or $-(CH_2)_hO(CH_2)_iOR^7$, wherein each R^{10} group is optionally substituted by up to three groups independently selected from R^{16};

R^{11} is a heterocyclic group having the following structure:



or



R^{12} is hydrogen or C_{1-6}alkyl;

R^{13} is hydrogen or C_{1-4}alkyl substituted by a group selected from optionally substituted phenyl, optionally substituted 5 or 6 membered heteroaryl and optionally substituted 9 to 10 membered fused bicyclic heteroaryl;

R^{14} and R^{15} are each independently hydrogen or C_{1-6}alkyl;

R^{16} is halogen, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{21}$, $-C(O)OR^{21}$, $-OC(O)R^{21}$, $-OC(O)OR^{21}$, $-NR^{22}C(O)R^{23}$, $-C(O)NR^{22}R^{23}$, $-NR^{22}R^{23}$, hydroxy, C_{1-6}alkyl, $-S(O)_kC_{1-}$

$_{6}$alkyl, C_{1-6}alkoxy, -$(CH_2)_m$aryl or -$(CH_2)_m$heteroaryl, wherein the alkoxy group is optionally substituted by up to three groups independently selected from -$NR^{14}R^{15}$, halogen and -OR^{14}, and the aryl and heteroaryl groups are optionally substituted by up to five groups independently selected from halogen, cyano, nitro, trifluoromethyl, azido, -$C(O)R^{24}$, -$C(O)OR^{24}$, -$OC(O)OR^{24}$, -$NR^{25}C(O)R^{26}$, -$C(O)NR^{25}R^{26}$, -$NR^{25}R^{26}$, hydroxy, C_{1-6}alkyl and C_{1-6}alkoxy;

R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl or a 5 or 6 membered heterocyclic group, wherein the alkyl, cycloalkyl, alkenyl and heterocyclic groups are optionally substituted by up to three substituents independently selected from optionally substituted 5 or 6 membered heterocyclic group, optionally substituted 5 or 6 membered heteroaryl, -OR^{27}, -$S(O)_nR^{27}$, -$NR^{27}R^{28}$, -$CONR^{27}R^{28}$, halogen and cyano;

R^{18} is hydrogen, -$C(O)OR^{29}$, -$C(O)NHR^{29}$ or -$C(O)CH_2NO_2$;

R^{19} is hydrogen, C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy, C_{3-7}cycloalkyl, or optionally substituted phenyl or benzyl;

R^{20} is halogen, C_{1-4}alkyl, C_{1-4}thioalkyl, C_{1-4}alkoxy, -NH_2, -$NH(C_{1-4}alkyl)$ or -$N(C_{1-4}alkyl)_2$;

R^{21} is hydrogen, C_{1-10}alkyl, -$(CH_2)_p$aryl or -$(CH_2)_p$heteroaryl;

R^{22} and R^{23} are each independently hydrogen, -OR^{14}, C_{1-6}alkyl, -$(CH_2)_q$aryl or -$(CH_2)_q$heterocyclyl;

R^{24} is hydrogen, C_{1-10}alkyl, -$(CH_2)_r$aryl or -$(CH_2)_r$heteroaryl;

R^{25} and R^{26} are each independently hydrogen, -OR^{14}, C_{1-6}alkyl, -$(CH_2)_s$aryl or -$(CH_2)_s$heterocyclyl;

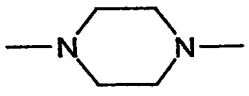
R^{27} and R^{28} are each independently hydrogen, C_{1-4}alkyl or $C_{1-4}alkoxyC_{1-4}$alkyl;

R^{29} is hydrogen or C_{1-6}alkyl optionally substituted by up to three groups independently selected from halogen, C_{1-4}alkoxy, -$OC(O)C_{1-6}$alkyl and -$OC(O)OC_{1-6}$alkyl;

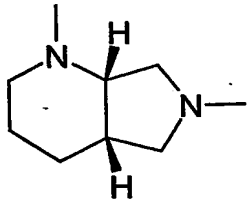
R^{30} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, optionally substituted phenyl or benzyl, acetyl or benzoyl;

R^{31} is hydrogen or R^{20}, or R^{31} and R^{19} are linked to form the bivalent radical -$O(CH_2)_2$- or -$(CH_2)_t$-;

X is -$U(CH_2)_vB$-, -$U(CH_2)_v$- or a group selected from:



and



U and B are independently a divalent radical selected from $-N(R^{30})-$, $-O-$, $-S(O)_z-$, $-N(R^{30})C(O)-$, $-C(O)N(R^{30})-$ and $-N[C(O)R^{30}]-$;
W is $-C(R^{31})-$ or a nitrogen atom;
d is an integer from 2 to 6;
e is an integer from 2 to 4;
f, g, h, m, p, q, r and s are each independently integers from 0 to 4;
i is an integer from 1 to 6;
j, k, n and z are each independently integers from 0 to 2;
t is 2 or 3;
v is an integer from 2 to 8;
and pharmaceutically acceptable derivatives thereof.

The term "pharmaceutically acceptable" as used herein means a compound which is suitable for pharmaceutical use. Salts and solvates of compounds of the invention which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of the invention and their pharmaceutically acceptable salts and solvates.

The term "pharmaceutically acceptable derivative" as used herein means any pharmaceutically acceptable salt, solvate or prodrug, e.g. ester, of a compound of the invention, which upon administration to the recipient is capable of providing (directly or indirectly) a compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives. Preferred pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. Particularly preferred pharmaceutically acceptable derivatives are salts, solvates and esters. Most preferred pharmaceutically acceptable derivatives are salts and esters.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. For example, an aqueous solution of an acid such as hydrochloric acid may be added to an aqueous suspension of a compound of formula (I) and the resulting mixture evaporated to dryness (lyophilised) to obtain the acid addition salt as a solid. Alternatively, a compound of

formula (I) may be dissolved in a suitable solvent, for example an alcohol such as isopropanol, and the acid may be added in the same solvent or another suitable solvent. The resulting acid addition salt may then be precipitated directly, or by addition of a less polar solvent such as diisopropyl ether or hexane, and isolated by filtration.

Suitable addition salts are formed from inorganic or organic acids which form non-toxic salts and examples are hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, trifluoroacetate, maleate, malate, fumarate, lactate, tartrate, citrate, formate, gluconate, succinate, pyruvate, oxalate, oxaloacetate, trifluoroacetate, saccharate, benzoate, alkyl or aryl sulphonates (eg methanesulphonate, ethanesulphonate, benzenesulphonate or p-toluenesulphonate) and isethionate. Representative examples include trifluoroacetate and formate salts, for example the bis or tris trifluoroacetate salts and the mono or diformate salts.

Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases, including salts of primary, secondary and tertiary amines, such as isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexyl amine and N-methyl-D-glucamine.

Compounds of the invention may have both a basic and an acidic centre may therefore be in the form of zwitterions.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention. The salts of the compound of formula (I) may form solvates (e.g. hydrates) and the invention also includes all such solvates.

The term "prodrug" as used herein means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, "Prodrugs as Novel Delivery Systems", Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., "Bioreversible Carriers in Drug Design", American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

Prodrugs are any covalently bonded carriers that release a compound of structure (I) *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by

modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I). Further, in the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like. Esters may be active in their own right and/or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable derivatives.

With regard to stereoisomers, the compounds of structure (I) have more than one asymmetric carbon atom. In the general formula (I) as drawn, the solid wedge shaped bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

It will be appreciated that the substituents on the macrolide may also have one or more asymmetric carbon atoms. Thus, the compounds of structure (I) may occur as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

Where a compound of the invention contains an alkenyl group, cis (Z) and trans (E) isomerism may also occur. The present invention includes the individual stereoisomers of the compound of the invention and, where appropriate, the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. A stereoisomeric mixture of the agent may also be prepared from a corresponding optically pure intermediate or by resolution, such as H.P.L.C., of the corresponding mixture using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding mixture with a suitable optically active acid or base, as appropriate.

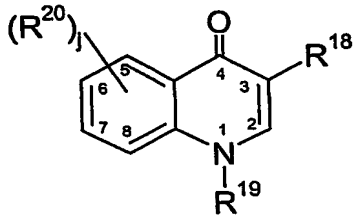
The compounds of structure (I) may be in crystalline or amorphous form. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention.

Compounds wherein R^2 represents a hydroxyl protecting group are in general intermediates for the preparation of other compounds of formula (I).

When the group OR^2 is a protected hydroxyl group this is conveniently an ether or an acyloxy group. Examples of particularly suitable ether groups include those in which R^2 is a trialkylsilyl (i.e. trimethylsilyl). When the group OR^2 represents an acyloxy group, then examples of suitable groups R^2 include acetyl or benzoyl.

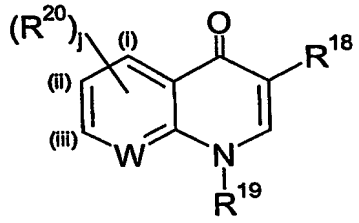
R^6 is hydrogen or fluorine. However, it will be appreciated that when A is -C(O)NH- or -CH_2-N(R^7)-, R^6 is hydrogen.

When R^{11} is a heterocyclic group having the following structure:



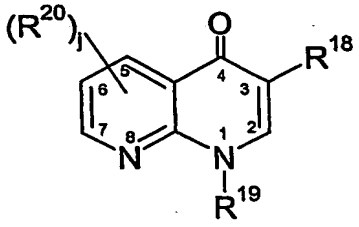
said heterocyclic is linked in the 5, 6, 7 or 8 position to the X group as above defined. In one embodiment, the heterocyclic is linked in the 6 or 7 position. In another embodiment, the heterocyclic is linked in the 5 or 8 position. When present, the R^{20} group or groups may be attached at any position on the ring. In one embodiment, an R^{20} group is attached at the 6 or 7 position.

When R^{11} is a heterocyclic group having the following structure:



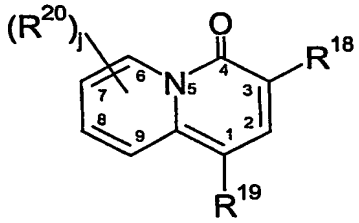
wherein W is -C(R^{31})- where R^{31} is R^{20} or R^{31} and R^{19} are linked to form the bivalent radical -O(CH_2)$_2$- or -(CH_2)$_t$-, said heterocyclic is linked in the (i), (ii) or (iii) position to the X group as above defined. In one embodiment, the heterocyclic is linked in the (i) position. In another embodiment, the heterocyclic is linked in the (ii) or (iii) position.

When R^{11} is a heterocyclic group having the following structure:



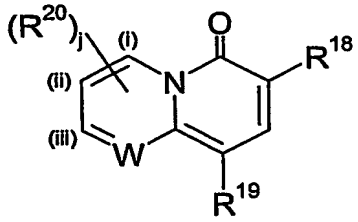
said heterocyclic is linked in the 5, 6 or 7 position to the X group as defined above. In one embodiment, the heterocyclic is linked in the 6 or 7 position. In another embodiment, the heterocyclic is linked in the 5 position. The R^{20} group or groups may be attached at any position on the ring. In one embodiment, an R^{20} group is attached at the 6 position.

When R^{11} is a heterocyclic group having the following structure:



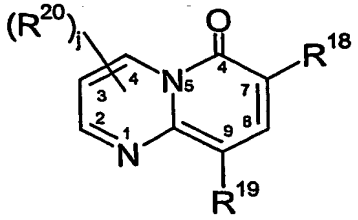
said heterocyclic is linked in the 6, 7, 8 or 9 position to the X group as above defined. In one embodiment, the heterocyclic is linked in the 7 or 8 position. In another embodiment, the heterocyclic is linked in the 6 or 9 position.

When R^{11} is a heterocyclic group having the following structure:



wherein W is $-C(R^{31})-$ where R^{31} is R^{20} or R^{31} and R^{19} are linked to form the bivalent radical $-O(CH_2)_2-$ or $-(CH_2)_t-$, said heterocyclic is linked in the (i), (ii) or (iii) position to the X group as above defined. In one embodiment, the heterocyclic is linked in the (i) position. In another embodiment, the heterocyclic is linked in the (ii) or (iii) position.

When R^{11} is a heterocyclic group having the following structure:



said heterocyclic is linked in the 2, 3 or 4 position to the X group as above defined. In one embodiment, the heterocyclic is linked in the 2 or 3 position. In another embodiment, the heterocyclic is linked in the 4 position.

The term "alkyl" as used herein as a group or a part of a group refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms. For example, C_{1-10}alkyl means a straight or branched alkyl containing at least 1, and at most 10, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, t-butyl, hexyl, heptyl, octyl, nonyl and decyl. A C_{1-4}alkyl group is preferred, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or t-butyl.

The term "C_{3-7}cycloalkyl" group as used herein refers to a non-aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "alkoxy" as used herein refers to a straight or branched chain alkoxy group containing the specified number of carbon atoms. For example, C_{1-6}alkoxy means a straight or branched alkoxy containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy and hexyloxy. A C_{1-4}alkoxy group is preferred, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or 2-methylprop-2-oxy.

The term "alkenyl" as used herein as a group or a part of a group refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms and containing at least one double bond. For example, the term "C_{2-6}alkenyl" means a straight or branched alkenyl containing at least 2, and at most 6, carbon atoms and containing at least one double bond. Examples of "alkenyl" as used herein include, but are not limited to, ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-methylbut-2-enyl, 3-hexenyl and 1,1-dimethylbut-2-enyl. It will be appreciated that in groups of the form -O-C_{2-6}alkenyl, the double bond is preferably not adjacent to the oxygen.

The term "aryl" as used herein refers to an aromatic carbocyclic moiety such as phenyl, biphenyl or naphthyl.

The term "heteroaryl" as used herein, unless otherwise defined, refers to an aromatic heterocycle of 5 to 10 members, having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono and bicyclic ring systems. Examples of heteroaryl rings include, but are not limited to, furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzimidazolyl, benzothienyl, benzoxazolyl, 1,3-benzodioxazolyl, indolyl, benzothiazolyl, furylpyridine, oxazolopyridyl and benzothiophenyl.

The term "5 or 6 membered heteroaryl" as used herein as a group or a part of a group refers to a monocyclic 5 or 6 membered aromatic heterocycle containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples include, but are not limited to, furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl and triazinyl.

The term "9 to 10 membered fused bicyclic heteroaryl" as used herein as a group or a part of a group refers to quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzimidazolyl, benzothienyl, benzoxazolyl, 1,3-benzodioxazolyl, indolyl, benzothiazolyl, furylpyridine, oxazolopyridyl or benzothiophenyl.

The term "heterocyclyl" as used herein, unless otherwise defined, refers to a monocyclic or bicyclic three- to ten-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the heterocyclyl ring has five or six ring atoms. Examples of heterocyclyl groups include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholino, tetrahydropyranyl and thiomorpholino.

The term "5 or 6 membered heterocyclic group" as used herein as a group or part of a group refers to a monocyclic 5 or 6 membered saturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples of such heterocyclyl groups include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholino, tetrahydropyranyl and thiomorpholino.

The term "halogen" refers to a fluorine, chlorine, bromine or iodine atom.

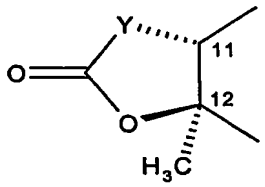
The terms "optionally substituted phenyl", "optionally substituted phenyl or benzyl", "optionally substituted 5 or 6 membered heteroaryl", "optionally substituted 9 to 10 membered fused bicyclic heteroaryl" or "optionally substituted 5 or 6 membered heterocyclic group" as used herein refer to a group which is substituted by 1 to 3 groups selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxy, nitro, cyano, amino, C_{1-4}alkylamino or diC_{1-4}alkylamino, phenyl and 5 or 6 membered heteroaryl.

In one embodiment, A is -C(O)-, -C(O)NH-, -NHC(O)-, -N(R^7)-CH_2-, -CH_2-N(R^7)- or -CH(NR^8R^9)-. In another embodiment, A is -C(O)-, -C(O)NH-, -NHC(O)-, -CH_2-N(R^7)-, -CH(NR^8R^9)- or -C(=NR^{10})-. In a further embodiment, A is -C(O)-, -C(O)NH-, -NHC(O)-, -CH_2-NR^7- or -CH(NR^8R^9)-. Representative examples of A include -C(O)- and -N(R^7)-CH_2-. In particular, A is -C(O)-.

A representative example of R^2 is hydrogen.

Representative examples of R^3 include hydrogen and C_{1-4}alkyl, for example hydrogen and methyl. In particular, R^3 is methyl.

In one embodiment, R^4 and R^5 are hydroxy. Alternatively, R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:

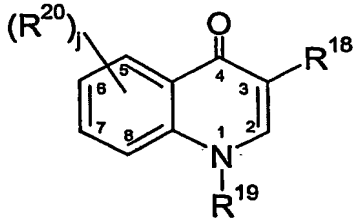


wherein Y is a bivalent radical selected from -O- and -N(R^{13})-.

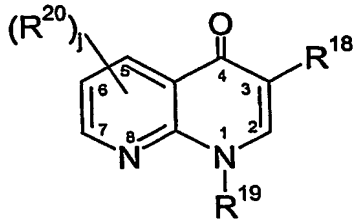
A representative example of R^6 is hydrogen.

A representative example of R^7 is C_{1-6}alkyl, for example C_{1-4}alkyl, in particular methyl.

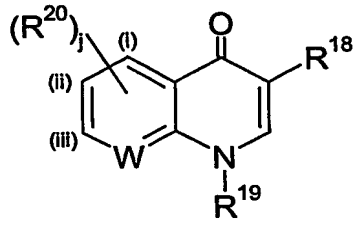
Representative examples of R^{11} include heterocyclic groups having the following structures:



and



wherein the heterocyclic is linked in the 6 or 7 position to the X group as above defined, and heterocyclic groups having the following structure:



wherein W is -C(R^{31})- and R^{31} and R^{19} are linked to form the bivalent radical -$(CH_2)_t$-, and the heterocylic is linked in the (ii) or (iii), position to the X group as above defined.

Representative examples of R^{13} include hydrogen and C_{1-4}alkyl, for example hydrogen and methyl.

In one embodiment, R^{18} is -C(O)OR^{29}, -C(O)NHR^{29} or -C(O)CH_2NO_2. A representative example of R^{18} is -C(O)OR^{29}, wherein R^{29} is hydrogen.

Representative examples of R^{19} include C_{1-4}alkyl, in particular ethyl, and C_{3-7}cycloalkyl, in particular cyclopropyl.

Representative examples of R^{20} include halogen, in particular chlorine or fluorine.

Representative examples of R^{30} include hydrogen and C_{1-4}alkyl, in particular hydrogen and methyl.

A representative example of R^{31} is hydrogen, or R^{31} and R^{19} are linked to form the divalent radical -$(CH_2)_t$-.

Representative examples of X are -$U(CH_2)_VB$- and -$U(CH_2)_V$-.

Representative examples of U and B include the divalent radicals -N(R^{30})-, -O- and -$S(O)_Z$-. In particular, U is -N(R^{30})- and B is selected from the divalent radicals -N(R^{30})-, -O- and -$S(O)_Z$-.

Representative examples of d include 2 and 3.

A representative example of t is 3.

A representative example of v is 2 to 4, in particular 2 or 3.

A representative example of z is 0.

Representative examples of j include 0 and 1.

Particularly preferred compounds of the invention are:
4"-*O*-(2-{[2-(3-carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethyl]-methylamino}-ethyl)-6-*O*-methyl-erythromycin A 11,12-carbonate;
4"-*O*-(3-{[2-(3-carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)ethyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate;
4"-*O*-{3-[2-(2-carboxy-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-9-yloxy)-ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate;
4"-*O*-(3-{[3-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)propyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate;
4"-*O*-(3-{[2-(3-carboxy-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridin-7-ylamino)ethyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate;
and pharmaceutically acceptable derivatives thereof.

Compounds according to the invention also exhibit a broad spectrum of antimicrobial activity, in particular antibacterial activity, against a wide range of clinical pathogenic microorganisms. Using a standard microtiter broth serial dilution test, compounds of the invention have been found to exhibit useful levels of activity against a wide range of pathogenic microorganisims. In particular, the compounds of the invention may be active against strains of Staphylococcus aureus, Streptopococcus pneumoniae, Moraxella catarrhalis, Streptococcus pyogenes, Haemophilus influenzae, Enterococcus faecalis, Chlamydia pneumoniae, Mycoplasma pneumoniae and Legionella pneumophila. The compounds of the invention may also be active against resistant strains, for example erythromycin resistant strains. In particular, the compounds of the invention may be active against erythromycin resistant strains of Streptococcus pneumoniae, Streptococcus pyogenes and Staphylococcus aureus.

The compounds of the invention may therefore be used for treating a variety of diseases caused by pathogenic microorganisms, in particular bacteria, in human beings and animals. It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

Thus, according to another aspect of the present invention we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in therapy.

According to a further aspect of the invention we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the therapy or prophylaxis of systemic or topical microbial infections in a human or animal subject.

According to a further aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment or prophylaxis of systemic or topical microbial infections in a human or animal body.

According to a yet further aspect of the invention we provide a method of treatment of the human or non-human animal body to combat microbial infections comprising administration to a body in need of such treatment of an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation eg when the agent is in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

Accordingly, in one aspect, the present invention provides a pharmaceutical composition or formulation comprising at least one compound of the invention or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable excipient, diluent and/or carrier. The excipient, diluent and/or carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, at least one compound of the invention or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable excipient, diluent and/or carrier for use in therapy, and in particular, in the treatment of human or animal subjects suffering from a condition susceptible to amelioration by an antimicrobial compound.

In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compounds of the present invention and a pharmaceutically acceptable excipient, diluent and/or carrier (including combinations thereof).

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of the invention or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable excipient, diluent and/or carrier.

The compounds of the invention may be formulated for administration in any convenient way for use in human or veterinary medicine and the invention therefore includes within its scope pharmaceutical compositions comprising a compound of the invention adapted for use in human or veterinary medicine. Such compositions may be presented for use in a conventional manner with the aid of one or more suitable excipients, diluents and/or carriers. Acceptable excipients, diluents and carriers for therapetic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical excipient, diluent and/or carrier can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as – or in addition to – the excipient, diluent and/or carrier any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s).

Preservatives, stabilisers, dyes and even flavouring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

For some embodiments, the agents of the present invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e. g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO 91/11172, WO 94/02518 and WO 98/55148.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention may be prepared by processes known in the art, for example see International Patent Application No. WO 02/00196 (SmithKline Beecham).

The routes for administration (delivery) include, but are not limited to, one or more of: oral (e. g. as a tablet, capsule, or as an ingestable solution), topical, mucosal (e. g. as a

nasal spray or aerosol for inhalation), nasal, parenteral (e. g. by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, epidural and sublingual.

There may be different composition/formulation requirements depending on the different delivery systems. By way of example, the pharmaceutical composition of the present invention may be formulated to be delivered using a mini-pump or by a mucosal route, for example, as a nasal spray or aerosol for inhalation or ingestable solution, or parenterally in which the composition is formulated by an injectable form, for delivery, by, for example, an intravenous, intramuscular or subcutaneous route. Alternatively, the formulation may be designed to be delivered by both routes.

Where the agent is to be delivered mucosally through the gastrointestinal mucosa, it should be able to remain stable during transit though the gastrointestinal tract; for example, it should be resistant to proteolytic degradation, stable at acid pH and resistant to the detergent effects of bile.

Where appropriate, the pharmaceutical compositions can be administered by inhalation, in the form of a suppository or pessary, topically in the form of a lotion, solution, cream, ointment or dusting powder, by use of a skin patch, orally in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents, or they can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For parenteral administration, the compositions may be best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccharides to make the solution isotonic with blood. For buccal or sublingual administration the compositions may be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

It is to be understood that not all of the compounds need be administered by the same route. Likewise, if the composition comprises more than one active component, then those components may be administered by different routes.

The compositions of the invention include those in a form especially formulated for parenteral, oral, buccal, rectal, topical, implant, ophthalmic, nasal or genito-urinary use. For some applications, the agents of the present invention are delivered systemically (such as orally, buccally, sublingually), more preferably orally. Hence, preferably the agent is in a form that is suitable for oral delivery.

If the compound of the present invention is administered parenterally, then examples of such administration include one or more of: intravenously, intraarterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously administering the agent; and/or by using infusion techniques.

For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

The compounds according to the invention may be formulated for use in human or veterinary medicine by injection (e.g. by intravenous bolus injection or infusion or via intramuscular, subcutaneous or intrathecal routes) and may be presented in unit dose form, in ampoules, or other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, solubilising and/or dispersing agents. Alternatively the active ingredient may be in sterile powder form for reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The compounds of the invention can be administered (e. g. orally or topically) in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed-or controlled-release applications.

The compounds of the invention may also be presented for human or veterinary use in a form suitable for oral or buccal administration, for example in the form of solutions, gels, syrups, mouth washes or suspensions, or a dry powder for constitution with water or other suitable vehicle before use, optionally with flavouring and colouring agents. Solid compositions such as tablets, capsules, lozenges, pastilles, pills, boluses, powder, pastes, granules, bullets or premix preparations may also be used. Solid and liquid compositions for oral use may be prepared according to methods well known in the art. Such compositions may also contain one or more pharmaceutically acceptable carriers and excipients which may be in solid or liquid form.

The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as

polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia.

Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the invention may also be administered orally in veterinary medicine in the form of a liquid drench such as a solution, suspension or dispersion of the active ingredient together with a pharmaceutically acceptable carrier or excipient.

The compounds of the invention may also, for example, be formulated as suppositories e.g. containing conventional suppository bases for use in human or veterinary medicine or as pessaries e.g. containing conventional pessary bases.

The compounds according to the invention may be formulated for topical administration, for use in human and veterinary medicine, in the form of ointments, creams, gels, hydrogels, lotions, solutions, shampoos, powders (including spray or dusting powders), pessaries, tampons, sprays, dips, aerosols, drops (e.g. eye ear or nose drops) or pour-ons.

For application topically to the skin, the agent of the present invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water.

Alternatively, it can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds may also be dermally or transdermally administered, for example, by use of a skin patch.

For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

As indicated, the compound of the present invention can be administered intranasally or by inhalation and is conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a suitable propellant, e. g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134AT™) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the active compound, e. g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e. g. sorbitan trioleate.

Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound and a suitable powder base such as lactose or starch.

For topical administration by inhalation the compounds according to the invention may be delivered for use in human or veterinary medicine via a nebuliser.

The compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

When a compound of the invention or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. The compounds of the present invention may for example be used for topical administration with other active ingredients such as corticosteroids or antifungals as appropriate.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a

combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

When administration is sequential, either the compound of the invention or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

The compositions may contain from 0.01-99% of the active material. For topical administration, for example, the composition will generally contain from 0.01-10%, more preferably 0.01-1% of the active material.

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular individual may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual undergoing therapy.

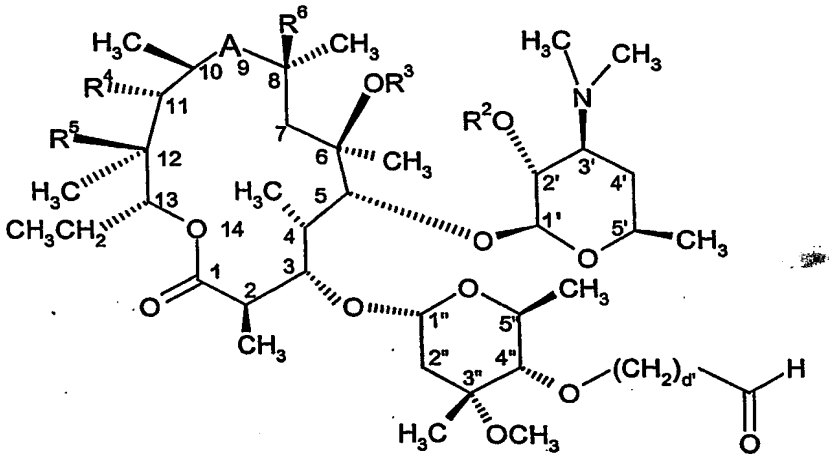
For oral and parenteral administration to humans, the daily dosage level of the agent may be in single or divided doses.

For systemic administration the daily dose as employed for adult human treatment it will range from 2-100mg/kg body weight, preferably 5-60mg/kg body weight, which may be administered in 1 to 4 daily doses, for example, depending on the route of administration and the condition of the patient. When the composition comprises dosage units, each unit will preferably contain 200mg to 1g of active ingredient. The duration of treatment will be dictated by the rate of response rather than by arbitrary numbers of days.

Compounds of general formula (I) and salts thereof may be prepared by the general methods outlined hereinafter, said methods constituting a further aspect of the invention. In the following description, the groups R^1 to R^{31}, A, B, X, Y, U, W, d, e, f, g, h, i, j, k, m, n, p, q, r, s, t, v and z have the meaning defined for the compounds of formula (I) unless otherwise stated.

The groups R^{11a}, B^aR^{11a} and X^aR^{11a} are R^{11}, BR^{11} and XR^{11} as defined for formula (I) or groups convertible to R^{11}, BR^{11} and XR^{11}. Conversion of such groups typically arises if a protecting group is needed during the reactions described below. A comprehensive discussion of the ways in which such groups may be protected and methods for cleaving the resulting protected derivatives is given by for example T.W. Greene and P.G.M Wuts in Protective Groups in Organic Synthesis 2nd ed., John Wiley & Son, Inc 1991 and by P.J. Kocienski in Protecting Groups, Georg Thieme Verlag 1994 which are incorporated herein by reference. Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl and acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz, and 9-fluorenylmethoxycarbonyl (Fmoc)), aliphatic urethane protecting groups (e.g. t-butyloxycarbonyl (Boc), isopropyloxycarbonyl and cyclohexyloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl and chlorotrityl). Examples of suitable oxygen protecting groups may include for example alkyl silyl groups, such as trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate. Hydroxy groups may be protected by reaction of for example acetic anhydride, benzoic anhydride or a trialkylsilyl chloride in an aprotic solvent. Examples of aprotic solvents are dichloromethane, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and the like.

Compounds of formula (I) wherein U is -N(R^{30})- may be prepared by reaction of a 4" aldehyde compound of formula (II) wherein A, R^2, R^3, R^4 and R^5 may be suitably protected, for example by cyclic protection between the 9 and 12 positions when A is -C(O)- and d' is an integer from 1 to 5, with a suitable protected derivative of the amine (IIIa) or (IIIb), followed where necessary by subsequent removal of the hydroxyl protecting group R^2 and conversion of the B^aR^{11a} or R^{11a} group to BR^{11} or R^{11}.



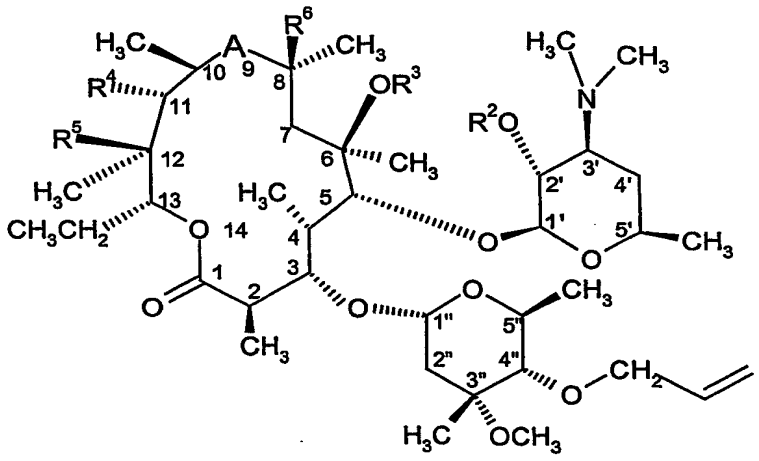
(II)

$HN(R^{30})(CH_2)_vB^aR^{11a}$ (IIIa)

$HN(R^{30})(CH_2)_vR^{11a}$ (IIIb)

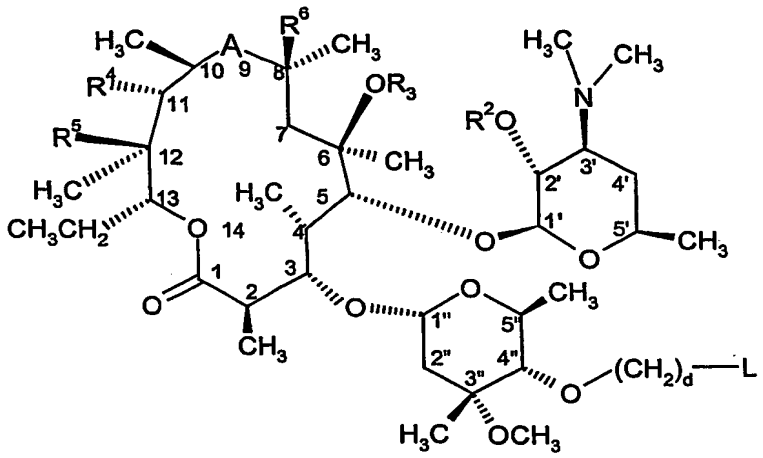
The reductive amination reaction is preferably carried out in a solvent such as methanol and DMF. A suitable reducing agent is, for example, sodium cyanoborohydride.

Compounds of formula (II) where d' is 1 or 2 may be prepared from suitably protected compounds of formula (IV) by hydroboration with 9-BBN, or other suitable boranes, followed by treatment with peroxide and then oxidation (d' = 2), or by osmium tetroxide/peridoate cleavage (d' = 1). Compounds of formula (IV) can be formed by palladium-catalysed allylation of suitably protected 4" hydroxy compounds.



(IV)

In a further embodiment of the invention, compounds of formula (I) wherein U is a group selected from -N(R^{30})- and -S-, may be prepared by reaction of compounds of formula (V)



(V)

wherein d is an integer from 2 to 6 and L is a suitable leaving group, with X^aR^{11a} (VI) in which U is a group selected from -N(R^{30})- and -S-. The reaction is preferably carried out in a solvent such as a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran or dimethoxyethane), acetonitrile or ethyl acetate and the like, dimethylsulfoxide, N,N-dimethylformamide or 1-methyl-pyrrolidone and in the presence of a base, followed, if desired, by removal of the hydroxyl protecting group R^2 and conversion of the X^aR^{11a} group to XR^{11}. Examples of the bases which may be used include organic bases such as diisopropylethylamine, triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and inorganic bases such as potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxide, sodium hydride, potassium hydride and the like. Suitable leaving groups for this reaction include halide (e.g. chloride, bromide or iodide) or a sulfonyloxy group (e.g. tosyloxy or methanesulfonyloxy).

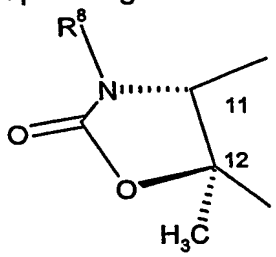
Compounds of formula (I) may be converted into other compounds of formula (I). Thus compounds of formula (I) wherein U or B is -$S(O)_z$- and z is 1 or 2 may be prepared by oxidation of the corresponding compound of formula (I) wherein z is 0. The oxidation is preferably carried out using a peracid, e.g. peroxybenzoic acid, followed by treatment with a phosphine, such as triphenylphosphine. The reaction is suitably carried out in an organic solvent such as methylene chloride. Compounds of formula (I) wherein U or B is -N(R^{30})- and R^{30} is C_{1-4}alkyl can be prepared from compounds wherein R^{30} is hydrogen by reductive alkylation.

Compounds of formula (II) wherein A is -C(O)NH- or -NHC(O)-, R^4 or R^5 are hydroxy, R^3 is hydrogen and R^6 is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 507595 and EP 503932.

Compounds of formula (II), wherein A is -C(O)NH- or -NHC(O)-, R^4 or R^5 are hydroxy and R^3 is C_{1-4}alkyl or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl and R^6 is hydrogen are known compounds or they may be prepared by

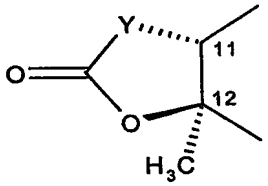
analogous methods to those known in the art. Thus they can be prepared according to the procedures described in WO 9951616 and WO 0063223.

Compounds of formula (II), wherein A is -C(O)NH-, R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:



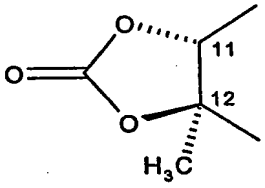
R^3 is C_{1-4}alkyl, or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl and R^6 is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in US 6262030.

Compounds of formula (II), wherein A is -C(O)-, -C(O)NH-, -NHC(O)-, -N(R^7)-CH_2-, -CH_2-N(R^7)- or -CH(NR^8R^9)-, R^4 or R^5 are hydroxy or R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:



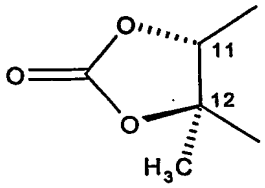
wherein Y is a bivalent radical selected from -O- and -N(R^{13})-, and R^3 is C_{1-4}alkyl, or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 307177, EP 248279, WO 0078773, WO 9742204.

Compounds of formula (II), wherein A is -C(O)NH-, -NHC(O)-, -N(CH_3)-CH_2- or -CH_2-N(CH_3)-, R^4 or R^5 are hydroxy or R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:



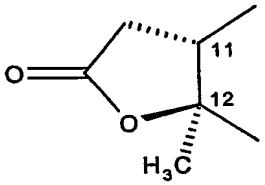
and R^6 is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 508699 and J.Chem. Res.Synop (1988 pages 152-153), US 6262030.

Compounds of formula (II), wherein A is -C(=NR^{10})-, R^4 or R^5 are hydroxy or R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:

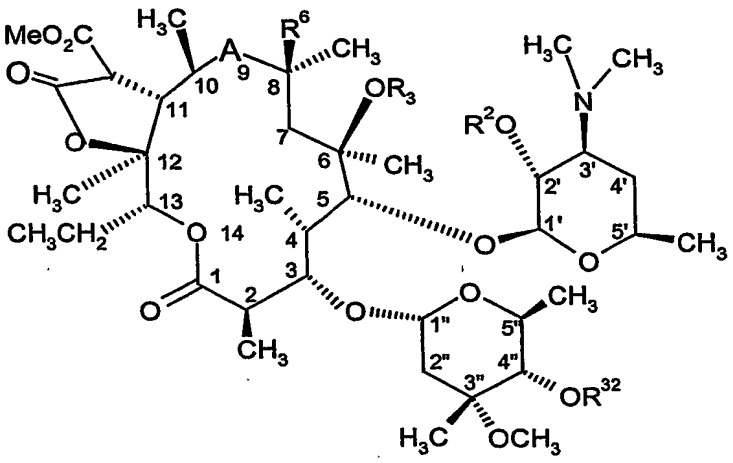


and R^6 is hydrogen, are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 284203.

Compounds of formula (II), wherein A is -C(O)-, R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:



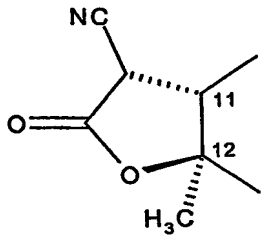
R^6 is hydrogen and R^3 is C$_{1-4}$ alkyl may be prepared by decarboxylation of a compound of formula (VII), wherein R^{32} is amino protecting group followed, if required, by removal of the protecting group R^2 or R^{32}.



(VII)

The decarboxylation may be carried out in the presence of a lithium salt such as lithium chloride, preferably in an organic solvent such as dimethylsulfoxide.

Compounds of formula (II), wherein A is -C(O)-, R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:



and R_3 is C_{1-4} alkyl may be prepared according to the procedures described in WO 02/50091 and WO 02/50092.

In order that the invention may be more fully understood the following examples are given by way of illustration only.

The following abbreviations are used in the text: 9-BBN for 9-borabicyclo[3.3.1]nonane, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, DCM for dichloromethane, DMF for N,N-dimethylformamide, DMSO for dimethyl sulfoxide, EtOH for ethanol, MeCN for acetonitrile, MeOH for methanol and THF for tetrahydrofuran.

Examples

Intermediate 1: 6-[(2-Aminoethyl)amino]-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

7-Chloro-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (56.3 g) and ethylenediamine (36 g) were dissolved in N,N-dimethylacetamide (650 mL) at 100°C and stirred for 8.5 h at 115°C. Water (700 mL) was added to the reaction mixture cooled at room temperature. The reaction mixture was stirred at room temperature for 2 h, cooled at 0-5°C and stirred for 1 h. The precipitate obtained was filtered, washed with cold water, cold EtOH, and dried at 110°C under reduced pressure for 1 h. The crude product was treated with HCl (6% aqueous solution) heating for 1 h in the presence of charcoal. After filtration, the solution was cooled to 35-40°C and a first precipitation happened. The precipitate was filtered, washed with water and dried at 110°C for 1 h. The title compound (6.4 g) was obtained as the hydrochloride salt. The hydrochloride salt was then converted to the free base using standard conditions; ESMS m/z 320 $[M-H]^-$.

Intermediate 2: 6-(2-Amino-ethoxy)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid hydrochloride

a) 6-(2-Dibenzylamino-ethoxy)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid 2-dibenzylamino-ethyl ester.

1-Ethyl-6-hydroxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (GB 1433774) (1.4 g, 6 mmol) was dissolved in dry DMF (80 mL). To this was added potassium carbonate (5 g, 36 mmol) and dibenzyl-(2-chloroethyl)amine hydrochloride (4.37 g, 14.8 mmol). The mixture was heated at 65°C with stirring for 72 h, then allowed to cool overnight. The mixture was evaporated to a small volume, diluted with water and extracted with ethyl acetate (x2). The combined organic extracts were washed with brine, dried and evaporated under reduced pressure to give a dark viscous oil (4.9 g). This residue was purified by chromatography on silica gel (100 g), eluting with 0.2 – 3.8% methanol in dichloromethane, to give the title compound as a brown solid (2.46 g, 60%); ESMS m/z 680 $[M+H]^+$ (100%).

b) 6-(2-Dibenzylamino-ethoxy)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid sodium salt.

Intermediate 2a (2.44 g, 3.59 mmol) was dissolved in methanol (25 mL) and 1,4-dioxane (25 mL), then aqueous sodium hydroxide (0.4N, 8.75 mL, 3.5 mmol) was added. Stirred for 40 h then a little more sodium hydroxide was added and stirring continued for a further 72 h. Excess solid carbon dioxide was then added and the mixture evaporated to dryness under reduced pressure. Trituration with diethyl ether gave the title compound as a pale brown powder (1.382 g, 84%); ESMS m/z 457 $[M+H]^+$ for the free acid (100%).

c) 6-(2-Amino-ethoxy)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid. **Intermediate 2b** (1.38 g, 2.89 mmol) was dissolved in 1,4-dioxane (80 mL), water (40 mL) and hydrochloric acid (2N, 2.9 mL, 5.8 mmol). This solution was hydrogenated over 20% palladium(II) hydroxide on carbon (0.6 g) at 50 psi for 18 h. The mixture was filtered through kieselguhr, washing well with water. The filtrate was then evaporated to dryness under reduced pressure to give the title compound as a pale yellow solid (1 g, 94%) (containing one equivalent of sodium chloride); ESMS m/z 277 $[M+H]^+$ for free acid (100%).

Intermediate 3: 6-(2-Aminoethylsulfanyl)-1-ethyl-4-oxo-1,4-dihydro-quinolone-3-carboxylic acid trifluoroacetate salt

a) 6-Bromo-1-ethyl-4-oxo-1,4-dihydro-quinolin-3-carboxylic acid ethyl ester.
A mixture of potassium carbonate (2.95 g, 21.2 mmol) and 6-bromoquinolone-3-carboxylic acid in dimethylformamide (25 mL) was heated to 40°C under argon for 10 minutes and iodoethane (3.4 mL, 42.4 mmol) was added. After 14 h the mixture was cooled and the DMF evaporated. The residue was treated with water (40 mL), cooled to 5°C and filtered under vacuum. The resultant cream-coloured solid was dried under vacuum to yield the title compound; ^{1}H NMR δ [$(CD_3)_2SO$] 1.41 (3H, t, J = 7.1 Hz), 1.54 (3H, J = 7.2 Hz), 4.24 (2H, q, J = 7.2 Hz), 4.40 (2H, q, J = 7.1 Hz), 7.34 (1H, d, J = 9 Hz), 7.76 (1H, dd, J = 2.4 & 9 Hz), 8.65 (1H, d, J = 2.4 Hz), 8.49 (1H, s).

b) 6-(2-*t*-Butoxycarbonylaminoethylsulfanyl)-1-ethyl-4-oxo-1,4-dihydro-quinolone-3-carboxylic acid ethyl ester.
A mixture of *N*-Boc-cysteinamine (0.35 g, 2 mmol), **Intermediate 3a** (0.32 g, 1 mmol) and potassium carbonate (0.28 g, 2 mmol) was heated in DMSO (10 ml) for 16 h at 90°C. After chromatography over silica gel eluting with dichloromethane containing an increasing concentration of methanol/ammonium hydroxide the title compound was obtained as a white solid; ESMS m/z 421 $[M+H]^+$ (100%).

c) 6-(2-*t*-Butoxycarbonylaminoethylsulfanyl)-1-ethyl-4-oxo-1,4-dihydro-quinolone-3-carboxylic acid sodium salt.
To a solution of **Intermediate 3b** (0.11 g, 0.27 mmol) in THF (2 mL) was added 2M sodium hydroxide (0.13 mL, 0.27 mmol). After stirring for 16 h at room temperature the mixture was saturated with carbon dioxide and the solvent evaporated. The residue was treated with methanol (10 mL), filtered and the solvent evaporated to yield the title compound as a pale yellow solid; ESMS m/z 393 $[M+H]^+$ (25%).

d) 6-(2-Aminoethylsulfanyl)-1-ethyl-4-oxo-1,4-dihydro-quinolone-3-carboxylic acid trifluoroacetate salt.
To **Intermediate 3c** (0.068 g, 0.17 mmol) was added trifluoroacetic acid (1 mL). After 1 h the solvent was evaporated to yield a green gum; ^{1}H NMR δ [$(CD_3)_2SO$] 1.54 (3H, t, J =

7.2 Hz), 3.20 (2H, q, J = 6.8 Hz), 3.38 (2H, t, J = 6.8 Hz), 4.56 (2H, q, J = 7.2 Hz), 7.98-7.90 (2H, m), 8.40 (1H, d, J = 2.0 Hz), 8.94 (1H, s).

Intermediate 4: 6-(3-Aminopropyl)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid trifluoroacetate salt

a) 1-Ethyl-6-iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester.

A mixture of 1,4-dihydro-6-iodo-4-oxo-quinoline-3-carboxylic acid (J. Ellis *et al*, *Aust. J. Chem.*, **1973**, *26*, 907) (3.15 g, 10 mmol), potassium carbonate (6.9 g, 50 mmol) and iodoethane (15.6 g, 100 mmol) in dry DMF was heated at 70°C with vigorous stirring. After 16 h the mixture was cooled and diluted with ethyl acetate. The resultant mixture was washed with water and the organic phase separated, dried and evaporated to yield the title compound as pale yellow solid, ^{1}H NMR δ ($CDCl_3$) 1.41 (3H, t, J = 7.1 Hz), 1.54 (3H, t, J = 7.3 Hz), 4.23 (2H, q, J = 7.2 Hz), 4.40 (2H, q, J = 7.1 Hz), 7.20 (1H, d, J = 8.9 Hz), 7.95 (1H, dd, J = 2.1 & 8.9 Hz), 8.48 (1H, s), 8.86 (1H, d, J = 2.1 Hz).

b) 6-(3-*t*-Butoxycarbonylamino-prop-1-ynyl)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester.

Intermediate 4a (0.371g, 1 mmol), copper (I) iodide (26 mg, 0.13 mmol) and triethylamine (6.16 mL, 44 mmol) were suspended in dry acetonitrile (22 mL). The light green suspension was heated to 50°C whilst argon was bubbled through. After 20 min, dichlorobis(triphenylphosphine)palladium (II) (0.026g, 0.0379 mmol) and *t*-butoxycarbonylpropargylamine (0.264 g, 1.7 mmol) were added and the brown suspension was heated under reflux. After 2 h the reaction mixture was cooled, filtered and concentrated. The residue was taken up in dichloromethane and washed with water. The organic phase was dried and concentrated to provide a brown oil which was purified by chromatography on silica gel eluting with 0-2.5% (9:1 MeOH/20 M ammonia) in dichloromethane to yield the title compound as a yellow solid; ESMS *m/z* 399 ($M+H^+$).

c) 6-(3-*t*-Butoxycarbonylaminopropyl)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester.

Intermediate 4b (0.366 mg, 0.77 mmol) in dichloromethane (10 mL) was hydrogenated over 10% palladium on charcoal (50 mg) for 16 h. The resultant mixture was filtered and the solvent evaporated to give the title compound as a yellow oil; ESMS *m/z* 403 $[M+H]^+$.

d) 6-(3-Aminopropyl)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester.

Using a similar procedure to that described in **Intermediate 3d**, **Intermediate 4c** (355 mg, 0.88 mmol) gave the title compound as a yellow oil; ESMS *m/z* 303 $[M+H]^+$.

e) 6-(3-Aminopropyl)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid sodium salt.

Using a similar procedure to that described in **Intermediate 3c**, **Intermediate 4d** (250 mg, 0.83 mmol) gave the title compound as a yellow solid; ESMS *m/z* 275 $[M+H]^+$.

f) 6-(3-Aminopropyl)-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid trifluoroacetate salt.

Intermediate 4e (0.06 g, 0.2 mmol) was subjected to reverse phase HPLC purification to give the title compound as white solid; ^{1}H NMR δ [$(CD_3)_2SO$] 1.54 (3H, t, J = 7.2 Hz), 2.0-2.1 (2H, m), 2.9-3.0 (4H, m), 4.58 (2H, q, J = 7.2 Hz), 7.85,(1H, dd, J = 2.2 & 8.8 Hz), 7.96 (1H, d, J = 8.8 Hz), 8.36 (1H, d, J = 1.8 Hz), 8.97 (1H, s).

Intermediate 5: 9-(2-Amino-ethoxy)-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid hydrochloride

a) 9-(2-Dibenzylamino-ethoxy)-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid 2-dibenzylamino-ethyl ester.

9-Hydroxy-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid (GB1417129) (0.905 g, 3.69 mmol) was suspended in dry DMF (50 mL). To this was added potassium carbonate (3.06 g, 22 mmol) and dibenzyl-(2-chloroethyl)amine hydrochloride (2.37 g, 8 mmol). The mixture was heated at 60°C for 16 h, then more potassium carbonate (0.55 g) and dibenzyl-(2-chloroethyl)amine hydrochloride (1.18 g, 4 mmol) were added. After a further 25 h at 75°C the mixture was evaporated. The residue was diluted with water and extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried and evaporated under reduced pressure. The crude product (4.0 g) was purified by chromatography on silica gel (100 g), eluting with 0 – 4% methanol in dichloromethane, to give the title compound (2.25 g, 89%); ESMS m/z 692 $[M+H]^+$ (100%).

b) 9-(2-Dibenzylamino-ethoxy)-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid sodium salt.

Intermediate 5a (2.22 g, 3.21 mmol) was dissolved in methanol (30 mL) and 1,4-dioxane (20 mL), and treated with aqueous sodium hydroxide (0.4N, 8.03 mL, 3.21 mmol). The mixture was stirred for 88 h at 20°C. Solid carbon dioxide was then added and the mixture evaporated to dryness under reduced pressure. The residue was triturated with diethyl ether to give the title compound as a white powder (1.6 g, 100%); ESMS m/z 469 $[M+H]^+$ for free acid (100%).

c) 9-(2-Amino-ethoxy)-1-oxo-6,7-dihydro-1H,5H-pyrido[3,2,1-ij]quinoline-2-carboxylic acid hydrochloride.

Intermediate 5b (0.8 g, 1.63 mmol) was dissolved in 1,4-dioxane (100 mL), water (15 mL) and hydrochloric acid (2N, 1.6 mL, 3.2 mmol). This solution was hydrogenated over 20% palladium(II) hydroxide on carbon (0.4 g) at 50 psi for 42 h. The mixture was diluted with water and filtered through kieselguhr, washing well with water. The filtrate was then

evaporated to dryness under reduced pressure to give the title compound as an off-white solid (0.54 g, 87%) (containing one equivalent of sodium chloride); ESMS m/z 289 $[M+H]^+$ for free acid (100%).

Intermediate 6: 7-(2-Amino-ethylamino)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid trifluoroacetate

a) 7-(2-*tert*-Butoxycarbonylamino-ethylamino)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester.

7-Chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester (2.20 g, 7.37 mmol) in THF (20 mL) and MeCN (20 mL) was treated with triethylamine (3.07 mL, 22.0 mmol), followed by (2-amino-ethyl)-carbamic acid *tert*-butyl ester (1.41 g, 8.80 mmol) and the mixture heated to 70°C. After 26 h (2-amino-ethyl)-carbamic acid *tert*-butyl ester (300 mg, 1.87 mmol) was added. After a further 15 h the heating was stopped and the solvent removed *in vacuo*. The residue was taken up in ethyl acetate, washed with water, dried filtered, and concentrated *in vacuo* to give a residue which was purified by chromatography (silica gel, 30-100% ethyl acetate in petroleum ether (b.p. 40-60°C)) to give the title compound (2.89 g); ESMS *m/z* 423 $[M+H]^+$.

b) 7-(2-*tert*-Butoxycarbonylamino-ethylamino)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid.

To **Intermediate 6a** (2.89 g, 6.84 mmol) in THF (30 mL) was added 2 N aqueous sodium hydroxide (3.4 mL, 6.8 mmol), and the mixture stirred at room temperature. After 24 h 2 N aqueous sodium hydroxide (0.6 mL, 1.2 mmol) was added and strirring continued for a further 24 h. The solvent was then removed *in vacuo*, and the residue taken up in water (10 mL). Solid carbon dioxide was added, and the resulting precipitate filtered off and dried in vacuo to give the title compound (2.65 g); ESMS *m/z* 395 $[M+H]^+$.

c) 7-(2-Amino-ethylamino)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid trifluoroacetate.

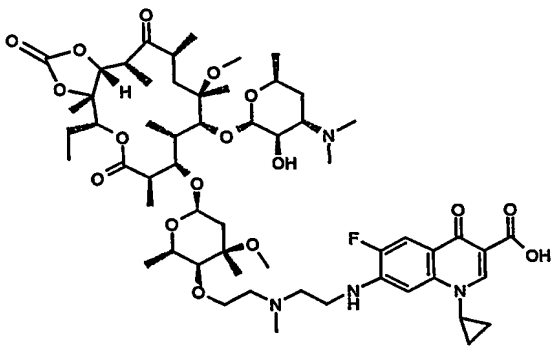
Intermediate 6b (2.65 g, 6.72 mmol) was suspended in dichloromethane (30 mL), trifluoroacetic acid (15 mL) added, and the solution stirred for 35 min. The mixture was concentrated *in vacuo*, and again from toluene, and again from hexane to give the title compound as a tan powder (2.92 g); ESMS *m/z* 295 $[M+H]^+$.

Intermediate 7: 2'-*O*-Acetyl-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate

6-O-Methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate (0.87 g) was dissolved in DCM (20 mL) and acetone (3 mL). Solid $NaHCO_3$ (0.6 g) and Ac_2O (0.6 mL) were added and the reaction mixture was stirred for 1 h, then DCM (50 mL) and

water (50 mL) were added. The organic phase was separated, washed with brine (20 mL), dried over K_2CO_3, filtered and concentrated under reduced pressure, affording the title compound (0.875 g); ESMS *m/z* 829 $[MH]^+$.

Example 1: 4"-*O*-(2-{[2-(3-Carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethyl]-methylamino}-ethyl)-6-*O*-methyl-erythromycin A 11,12-carbonate bis trifluoroacetate



a) 2'-*O*,3'-*N*-bis(Benzyloxycarbonyl)-3'-*N*-desmethyl-6-*O*-methyl-erythromycin A.
To a stirred mixture of 6-O-methyl-erythromycin A (20 g, 26.8 mmol) and sodium hydrogen carbonate (30 g) cooled in an ice bath was added portionwise benzyl chloroformate (60 mL). After 10 min the ice bath was removed and the mixture was stirred for 15 min. The reaction was then heated at 60-70°C for 1 h. After cooling, the reaction mixture was loaded onto a silica gel column (150 g) and eluted with a gradient of 10-50% ethyl acetate in hexane. Evaporation of the product containing fractions gave the title product as a white solid foam (20.22 g); ESMS *m/z* 1024 $[M+Na]^+$, 1060 $[M+NH4+acetonitrile]^+$.

b) 4"-*O*-Allyloxycarbonyl-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-desmethyl-6-*O*-methyl-erythromycin A 11,12-carbonate.
Example 1a (13 g, 12.97 mmol) in dichloromethane (50 mL) at 0°C under argon was added pyridine (11.5 mL) and a solution of phosgene in toluene (20%, 30 mL). After 30 min the mixture was allowed to warm to 20°C. After 2.5 h the reaction was recooled to 0°C and allyl alcohol (5 mL) was added dropwise. After stirring at 0°C for 15 min and 20°C for 30 min the mixture was poured onto ice. Extraction with diethyl ether and washing with water, 5% aq citric acid, and saturated aq sodium hydrogen carbonate gave a crude product solution which was dried, evaporated and purified by chromatography (silica gel, 20-50% ethyl acetate in hexane) to give the title product as a white solid foam (12.5 g); ESMS *m/z* 1129 $[M+NH4]^+$, 1134 $[M+Na]^+$, 1170 $[M+NH4+acetonitrile]^+$.

c) 4"-*O*-Allyl-2'-O,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-desmethyl-6-*O*-methyl-erythromycin A 11,12-carbonate.

Example 1b (7.9 g, 7.1 mmol) in tetrahydrofuran (50 mL) was treated with tetrakis(triphenylphosphine) palladium (0.16 g). The reaction was heated to reflux for 30 min after which time methyl allyl carbonate (1.7 mL) was added. After a further 1.75 h reflux, the reaction was cooled and evaporated to dryness. The residue was purified by chromatography (silica gel, 0-30% ethyl acetate in dichloromethane) to give the title product as a white solid foam (3.93 g); ESMS *m/z* 1085 $[M+NH4]^+$, 1090 $[M+Na]^+$, 1126 $[M+NH4+acetonitrile]^+$.

d) 2'-*O*, 3'-*N*-bis(Benzyloxycarbonyl)-4"-*O*-{2-[2-(3-Carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylamino]-ethyl}-6-*O*-methyl-3'-*N*-desmethyl-erythromycin A 11,12-carbonate.

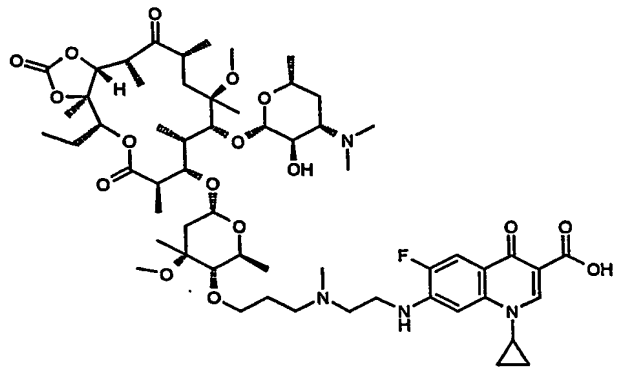
To **Example 1c** (0.256 g, 0.25 mmol) in tetrahydrofuran (1 mL) and water (1 mL) under argon was added osmium tetroxide (4% in water, 0.015 mL). After 5 min sodium periodate (0.213 g, 1 mmol) was added. After 2.5 h the mixture was diluted with diethyl ether and water. The organic phase was washed with saturated aq. sodium thiosulphate, dried, and evaporated to dryness to give the crude aldehyde as a white solid foam (0.255 g). This material (0.094 g) in methanol (1.5 mL) and dimethylformamide (1.5 mL) was treated with acetic acid (0.15 mL), 7-(2-aminoethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (Yoshida *et al*, *J. Pharm. Soc. Japan,* 1990, *110*, 258) (0.031 g, 0.1 mmol) and sodium cyanoborohydride (0.013 g, 0.2 mmol). After 3 h the reaction was evaporated to dryness, and the residue purified by chromatography (silica gel, 0-10% 2 M methanolic ammonia in dichloromethane) to give the title product as a white solid foam (0.066g); ESMS *m/z* 1359 $[M+H]^+$.

e) 4"-*O*-(2-{[2-(3-Carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethyl]-methylamino}-ethyl)-6-*O*-methyl-erythromycin A 11,12-carbonate bistrifluoroacetate.

Example 1d (0.066 g) in ethanol (20 mL) and dioxan (10 mL) was hydrogenated at 50 psi over palladium hydroxide (20% on carbon, 0.080 g) for 72 h. The catalyst was removed by filtration, washed well with dioxan and ethanol, and the combined filtrates evaporated to dryness. The residue was taken up in ethanol (20 mL) and dioxan (10 mL), and 28% aq formaldehyde (2 mL), 0.7min pH 4.5 acetate buffer (2 mL) and palladium hydroxide (20% on carbon, 0.080 g) added. The mixture was hydrogenated at 50 psi for a further 5 days, then the catalyst was removed by filtration, washed well with dioxan and ethanol, and the combined filtrates evaporated to dryness. The residue was purified by chromatography (silica gel, 5-10% methanol in dichloromethane then 10-20% 2 M methanolic ammonia in dichloromethane). Later fractions contained impure title product. Early eluted fractions contained 3'-*N*-benzyloxycarbonyl-4"-O-{2-[2-(3-carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylamino]-ethyl}-6-O-methyl-3'-*N*-desmethyl-erythromycin A 11,12-carbonate, (0.01 g) which was dissolved in ethanol (10 mL) and dioxan (5 mL) and hydrogenated at 50 psi over palladium (10% on carbon, 0.1 g). After 3 h 28% aq. formaldehyde (1.5 mL), 0.7M pH 4.5 acetate buffer (2.5 mL) was added and the

hydrogenation continued for 24 h. After filtration and evaporation, the residue was purified by chromatography (silica gel, 2-15% 2M methanolic ammonia in dichloromethane) giving impure product. Both batches of impure title product were purified by preparative HPLC (acetonitrile/water/0.1% trifluoroacetic acid eluent) to give the title compound as a gum (0.004 g); ESMS *m/z* 1119 $[M+H]^+$.

Example 2: 4"-*O*-(3-{[2-(3-Carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)ethyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate



a) 2'-*O*,3'-*N*-bis(Benzyloxycarbonyl)-4"-*O*-(3-hydroxypropyl)-3'-*N*-desmethyl-6-*O*-methyl-erythromycin A 11,12-carbonate.

Example 1c (0.97 g, 0.908mmol) in tetrahydrofuran (6 mL) was treated with 9-BBN (0.5M in tetrahydrofuran, 3.6 mL). After 1.5h the reaction was cooled to 0°C and sodium hydroxide (2 M, 1.5 mL) and hydrogen peroxide (27% in water, 2.1 mL) were added. After 5 min the cooling bath was removed and the reaction stirred for 15 m, then diluted with diethyl ether and water. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by chromatography (silica gel, 0-50% ethyl acetate in dichloromethane) to give the title product as a white solid foam (0.80 g, 76%); ESMS *m/z* 1103 $[M+NH4]^+$, 1108 $[M+Na]^+$.

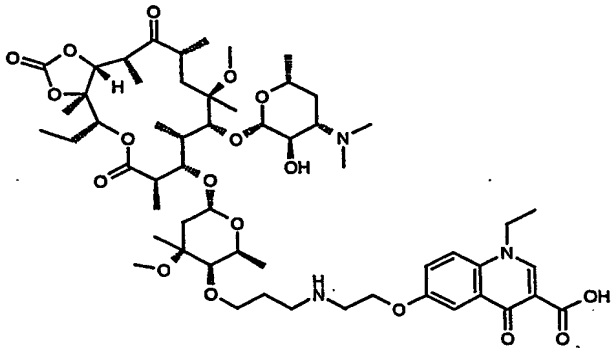
b) 2'-*O*,3'-*N*-bis(Benzyloxycarbonyl)-4"-O-{3-[2-(3-carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylamino]-propyl}]-6-O-methyl-3'-N-desmethyl-erythromycin A 11,12-carbonate trifluoroacetate.

To **Example 2a** (0.411 g, 0.378 mmol) in dichloromethane (6 mL) at 0°C under argon was added Dess-Martin periodinane (0.176 g, 0.41 mmol). After 1.5 h, the cooling bath was removed and the rection stirred for a further 30 min then diluted with dichloromethane, washed with saturated aq sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to dryness to give the title product as a white solid foam (0.42 g). This material (0.169 g) in methanol (2 mL) and dimethylformamide (2 mL) was treated with acetic acid (0.2 mL), 7-(2-aminoethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (0.048 g, 0.16 mmol) and sodium cyanoborohydride (0.02 g, 0.32 mmol). After 1.5 h the

reaction was evaporated to dryness, and the residue purified by preparative HPLC (acetonitrile/water/0.1% trifluoroacetic acid eluent) to give the title product (0.10 g); ESMS *m/z* 1373 $[M+H]^+$.

c) 4"-*O*-(3-{[2-(3-Carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate. **Example 2b** (0.1 g) in ethanol (20 mL) and dioxan (10 mL) was hydrogenated at 50 psi over palladium (10% on carbon, 0.050 g) for 7 h. 28% aq. Formaldehyde (2.5 mL), 0.7 M pH 4.5 acetate buffer (5 mL) was added and the hydrogenation continued for 24 h. After filtration and evaporation, dichloromethane (10 mL) and methanol (2 mL) were added to the residue and insoluble material removed by filtration. The soluble material was passed down a silica gel column eluting with 2-15% 2 M methanolic ammonia in dichloromethane. The fractions containing the title material were dissolved in ethanol (10 mL), 28% aq. formaldehyde (1 mL) and 0.7 M pH 4.5 acetate buffer (2 mL) and the mixture hydrogenated at 50 psi over palladium (10% on carbon, 0.1 g) for 30 h. The catalyst was removed by filtration and the residue evaporated to dryness. Dichloromethane (10 mL) and methanol (2 mL) were added to the residue and insoluble material removed by filtration. The soluble material was passed down a silica gel column eluting with 2-15% 2 M methanolic ammonia in dichloromethane to give the title product, as a gum (0.012 g); ^{1}H NMR (CD_3OD) (*inter alia*) 1.8 (2H, m), 2.4 (3H, s), 2.6 (2H, m), 2.8 (2H, m), 3.5 (2H, m), 3.7 (2H, m), 4.55 (1H, d), 4.65 (1H, s), 4.85 (1H, d), 5.0 (1H, dd), 7.2 (1H, d), 7.8 (1H, d), 8.7 (1H,s); ESMS *m/z* 1133 $[M+H]^+$.

Example 3: 4"-*O*-{3-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yloxy)-ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate bis trifluoroacetate



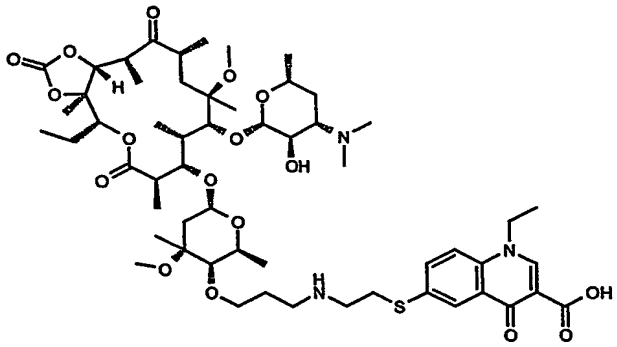
a) 4"-*O*-(3-Hydroxypropyl)-6-*O*-methyl-erythromycin A 11,12-carbonate. **Example 2a** (2.57 g, 2.37 mmol) in ethanol (25 mL) and dioxan (25 mL) was hydrogenated at 50 psi over palladium (10% on carbon, 0.2 g) for 26 h. The catalyst was removed by filtration and the soluble material taken up in ethanol (50 mL), pH 4.5 buffer (4 mL) and 37% aq formaldehyde solution (4 mL) were added and the mixture hydrogenated at 50 psi over palladium (10% on carbon, 0.5 g). After 18 h, the reaction mixture was

filtered, and the catalyst washed well with ethanol and dioxan. The combined filtrates were purified by chromatography on silica gel eluting with 0-10% 2 M methanolic ammonia in dichloromethane to give the title product as a white foam (1.21 g); ESMS *m/z* 832 $[M+H]^+$.

b) 4"-*O*-{3-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yloxy)-ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate bis trifluoroacetate.

To **Example 3a** (0.099 g, 0.119 mmol) in dichloromethane (2 mL) at 0°C under argon was added Dess-Martin periodinane (0.176 g, 0.41 mmol). After 15 min the reaction was allowed to warm to 20°C. After a total reaction time of 100 min the rection mixture was diluted with dichloromethane, washed with saturated. aq sodium hydrogen carbonate, dried, and evaporated to dryness to give the crude aldehyde as a white solid foam. This material was treated with acetic acid (0.1 mL), **Intermediate 2** (0.038 g, 0.12 mmol), sodium acetate (0.01 g) and sodium cyanoborohydride (0.015 g, 0.24 mmol). After 14 h the reaction was evaporated to dryness, and the residue partially purified by chromatography on silica gel eluting with 5-20% 2 M methanolic ammonia in dichloromethane followed by preparative HPLC (acetonitrile/water/0.1% trifluoroacetic acid eluent) to give the title product (0.013 g); ESMS *m/z* 1090 $[M+H]^+$.

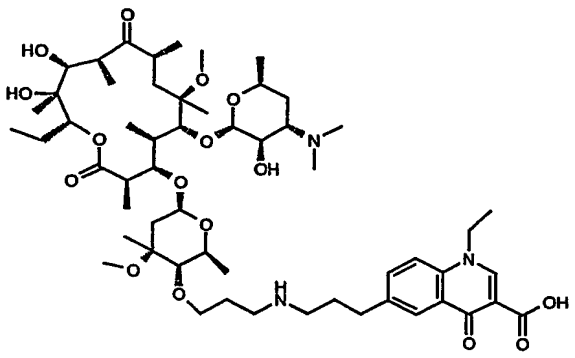
Example 4: 4"-*O*-{3-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-ylsulfanyl)-ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate bisformate



To **Example 3a** (0.125 g, 0.119 mmol) in dichloromethane (2.5 mL) under argon was added Dess-Martin periodinane (0.095 g, 0.22 mmol). After 3.5 h, the reaction mixture was diluted with dichloromethane, washed with saturated aq sodium hydrogen carbonate, dried, and evaporated to dryness to give the crude aldehyde as a white solid foam. This material was dissolved in dimethylformamide (1.5 mL) and methanol (1.5 mL) and treated with acetic acid (0.3 mL), Intermediate 3 (0.081 g, 0.2 mmol) sodium acetate (0.024 g) and sodium cyanoborohydride (0.015 g). After 3 h the reaction was evaporated to dryness, and the residue purified by preparative HPLC (acetonitrile/water/0.1% formic acid eluent) to give the title product (0.024 g); ^1H NMR δ ($CDCl_3$) (*inter alia*) 1.6 (3H, t),

2.0 (2H, m), 3.05 (2H, m), 3.65 (1H, m), 3.85 (1H, m), 4.4 (2H, q), 4.55(1H, d), 4.6 (1H, s), 4.85 (1H, d), 5.0 (1H, dd), 7.65 (1H, d), 7.85 (1H, d), 8.35 (2H, s), 8.4 (1H, s); ESMS *m/z* 1106 $[M+H]^+$.

Example 5: 4"-*O*-{3-[3-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-propylamino]-propyl}-6-*O*-methyl-erythromycin A bisformate



a) 4"-*O*-(1-Imidazol-1-yl-carbonyl)-6-*O*-methyl-erythromycin A.

6-*O*-Methyl-erythromycin A (30 g, 40.1 mmol) in tetrahydrofuran (100 mL) was treated portionwise with carbonyldiimidazole (16 g, 97 mmol) with ice bath cooling. After 1 h the cooling bath was removed. After a futher 48 h, tetrahydrofuran (100 mL) and water (200 mL) were added slowly precipitating the title compound, which was collected by filtration and dried to give the title compound (24.7 g). Extraction of the mother liquors with ether gave further material (8.5 g) which was precipitated from tetrahydrofuran solution with water to give a further portion of the title compound (3.92 g, total of 28.64 g); ESMS *m/z* 842 $[M+H]^+$.

b) 4"-*O*-(Allyloxycarbonyl)-6-*O*-methyl-erythromycin A.

Example 5a (28.64 g, 34 mmol) in dichloromethane (100 mL) was cooled to 0°C and treated with allyl alcohol (13.6 mL) and DBU (5.23 mL). The reaction was stirred at 0°C for 2.5 h and at 20°C for 1.75 h. The reaction mixture was quenched with 3% aq citric acid (100 mL), the phases separated, and the organic phase washed with sat sodium hydrogen carbonate and brine. After drying and evaporation to dryness, the residue was triturated with petroleum ether (bp 40-60 °C) to give the title compound as a solid (25.08 g); ESMS *m/z* 832 $[M+H]^+$.

c) 4"-*O*-(Allyloxycarbonyl)-9-dihydro-9-methoxy-9,12-anhydro-2',11-bis-*O*-trimethylsilyl-6-*O*-methyl-erythromycin A.

Example 5b (22.29 g, 25.6 mmol) in pyridine (100 mL) was treated with chlorotrimethylsilane (26 mL). The reaction was stirred at 20°C for 6 h and left at 4°C for 16 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue taken up in methanol (100 mL) After 80 min at 20°C, the solvent was removed by

evaporation under reduced pressure and the residue taken up in ethyl acetate and water. the phases were separated, the organic layer dried, and evaporated to dryness under reduced pressure. Toluene (two 500 mL portions) were added and evaporated under reduced pressure to give the crude title compound as a white foam (26.27 g). This material (5.8 g) was purified by chromatography on silica gel eluting with 0-3% 2 M methanolic ammonia in dichloromethane to give the title compound as a white foam (3.0 g); ESMS *m/z* 990 $[M+H]^+$.

d) 4"-*O*-Allyl-9-dihydro-9-methoxy-9,12-anhydro-2',11-bis-*O*-trimethylsilyl-6-*O*-methyl-erythromycin A.

Example 5c (3.0 g, 3.03 mmol) in tetrahydrofuran (20 mL) was treated with tetrakis triphenylphosphine palladium (0.1 g) at reflux under argon. After 35 min, *t*-butyl allyl carbonate (F. Houlihan *et al*, *Can. J. Chem.* 1985, *63*, 153; 1.2 mL) and tetrakis(triphenylphosphine) palladium (0.1 g) were added and the reflux continued for a further 1 h. The reaction was cooled and evaporated to dryness under reduced pressure, and the residue purified by chromatography on silica gel eluting with 0-5% 2 M methanolic ammonia in dichloromethane to give the title product, 1.07 g, as a white foam; ESMS *m/z* 946 $[M+H]^+$.

e) 4"-*O*-(3-Hydroxypropyl)-9-dihydro-9-methoxy-9,12-anhydro-2',11-bis-*O*-trimethylsilyl-6-*O*-methyl-erythromycin A.

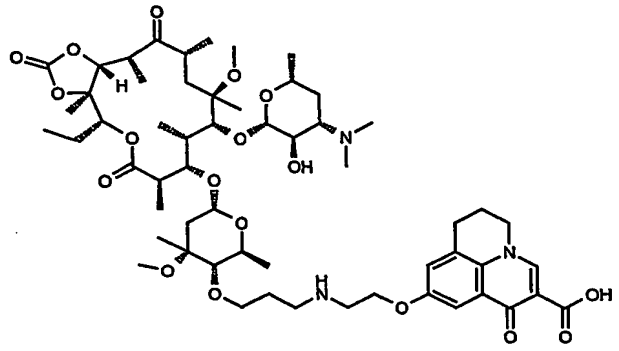
Example 5d (0.255 g, 0.27 mmol) in tetrahydrofuran (4 mL) under argon was treated with 9-BBN (0.5 M in tetrahydrofuran, 1.6 mL). After 30 min, the reaction was cooled to 0°C and a precooled mixture of sodium hydroxide (2 M, 0.5 mL) and hydrogen peroxide (27% in water, 0.68 mL) were added. This was stirred at 0°C for 10 min before addition of cold diethyl ether and water. The phases were separated and the organic phase washed with water and brine. After drying and evaporation under reduced pressure the residue was purified by chromatography on silica gel eluting with 0-10% 2 M methanolic ammonia in dichloromethane to give the title product as a white foam (0.16 g); ESMS *m/z* 964 $[M+H]^+$.

f) 4"-*O*-{3-[3-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-propylamino]-propyl}-6-*O*-methyl-erythromycin A bisformate.

To **Example 5e** (0.16 g, 0.166 mmol) in dichloromethane (5 mL) under argon was added Dess-Martin periodinane (0.085 g, 0.2 mmol). After 1 h, the rection mixture was diluted with dichloromethane, washed with sat. aq sodium hydrogen carbonate, dried, and evaporated to dryness to give the crude aldehyde as a gum. This material was dissolved in methanol (2.5 mL) and dichloromethane (2.5 mL) and treated with acetic acid (0.25 mL), sodium acetate (0.028 g), 3A molecular sieves (0.3 g), **Intermediate 4** (0.0625g, 0.16 mmol) and sodium cyanoborohydride (0.030 g). After 2 h the reaction was evaporated to dryness, and toluene (5 mL) added and evaporated. The residue was purified by preparative HPLC (acetonitrile/water/0.1% formic acid eluent) and the fractions allowed to stand at 20°C for 1 h which resulted in loss of protection. A further preparative

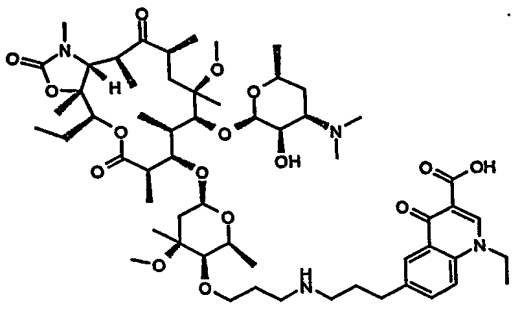
HPLC (acetonitrile/water/0.1% formic acid eluent) purification gave the title product (0.034 g); ESMS *m/z* 1062 $[M+H]^+$.

Example 6: 4"-*O*-{3-[2-(2-Carboxy-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-9-yloxy)-ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate bisformate



To **Example 3a** (0.25 g, 0.33 mmol) in dichloromethane (5 mL) under argon was added Dess-Martin periodinane (0.14 g, 0.33 mmol). After 2 h, more Dess-Martin periodinane (0.03 g) was added and the reaction stirred for a further 1.5 h. The reaction mixture was diluted with dichloromethane, washed with saturated. aq sodium hydrogen carbonate, dried, and evaporated to dryness to give the crude aldehyde as a white solid foam. This material (0.042 g, 0.05 mmol) in methanol / DCM (1:1, 2 mL) was added to sodium acetate (0.008 g, 0.1 mmol), acetic acid (0.1 mL), **Intermediate 5** (0.02 g, 80% pure, 0.05 mmol), and 3A molecular sieves (0.1 g). The mixture was stirred for 15 min then a solution of sodium cyanoborohydride (0.0063 g, 0.1 mmol) in methanol (0.2 mL) was added and stirring continued for 3 h. The reaction was then filtered, washing well with methanol, and the fitrate evaporated. The residue was purified by preparative reverse phase HPLC (MeCN/H2O/0.1%HCO2H eluent) to give the title compound as a pale yellow solid (0.031 g); ESMS *m/z* 1102 $[M+H]^+$.

Example 7: 4"-*O*-{3-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-propylamino]-propyl}-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate formate



a) 2'-*O*-Acetyl-4"-*O*-allyl-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate.

Intermediate 7 (0.315 g, 0.38 mmol), *t*-butyl allyl carbonate (0.079 g, 0.5 mmol) and tetrakis(triphenylphosphine) palladium (0.035 g, 0.03 mmol) in THF (10 mL) were refluxed for 4 h. More *t*-butyl allyl carbonate (0.079 g, 0.5 mmol) was added and refluxing continued for a further 2 h. More *t*-butyl allyl carbonate (0.04 g, 0.25 mmol) was added and refluxing continued for a further 1.5 h. The mixture was then evaporated to dryness and the residue purified by chromatography on silica gel (40 g). Elution with 0-4.5% '2 M NH_3 in methanol' in dichloromethane, gave the title compound (0.294 g); ESMS *m/z* 869 $[M+H]^+$.

b) 4"-*O*-Allyl-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate.

Example 7a (0.27 g, 0.31 mmol) in methanol (10 mL) was heated at 60°C for 8.5 h, 45°C for 15 h, and 60°C for 3 h. The mixture was then evaporated to dryness to give the title compound as a white solid (0.244 g); ESMS *m/z* 827 $[M+H]^+$.

c) 2'-*O*,3'-*N*-bis(Benzyloxycarbonyl)-3'-*N*-desmethyl-4"-*O*-allyl-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate.

Example 7b (0.24 g, 0.29 mmol) and sodium hydrogencarbonate (0.4 g) in benzyl chloroformate (2 mL) were heated at 60°C for 3 h. After cooling the mixture was purified by chromatography on silica gel (50 g). Elution with 0-50% ethyl acetate in petroleum ether gave the title compound as a white solid (0.272 g); ESMS *m/z* 1098 $[M+NH_4]^+$.

d) 2'-*O*,3'-*N*-bis(Benzyloxycarbonyl)-3'-*N*-desmethyl-4"-*O*-(3-hydroxypropyl)-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate.

Example 7c (0.27 g, 0.25 mmol) in THF (8 mL) was treated with 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 1.5 mL, 0.75 mmol). After 4 h more 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 0.5 mL, 0.25 mmol) was added. Further 1 h then more 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 1 mL, 0.5 mmol) was added. After 1 h more the solution was cooled in an ice bath then pre-mixed hydrogen peroxide (30% aq, 1.7 mL, 15 mmol) in sodium hydroxide (2 N, 2.5 mL, 5 mmol) was added. The cooling bath was removed and the mixture stirred for 0.5 h. The reaction was diluted with water

and extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried, and evaporated to give the crude product. This was purified by chromatography on silica gel (40 g), eluting with 30-80% ethyl acetate in petroleum ether, to give the title compound as a white solid (0.139 g); ESMS *m/z* 1116 $[M+NH_4]^+$.

e) 4"-*O*-(3-Hydroxypropyl)-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate.

Example 7d (0.137 g, 0.125 mmol) was disolved in ethanol (4 mL) and 1,4-dioxane (6 mL), and hydrogenated over 10% palladium on charcoal (50% aq paste, 0.06 g) for 6.5h. Formaldehyde (37% aq, 0.3 ml), pH 4.5 acetate buffer (0.3 mL) and more catalyst (0.05 g) were then added, and the mixture hydrogenated for 16 h. The mixture was then filtered, washing well with ethanol and 1,4-dioxane. The filtrate was evaporated, and the residue purified by chromatography on silica gel (5 g). Elution with 0-6% '2 M NH_3 in methanol' in dichloromethane, gave the title compound as a white foam (0.083 g); ESMS *m/z* 845 $[M+H]^+$.

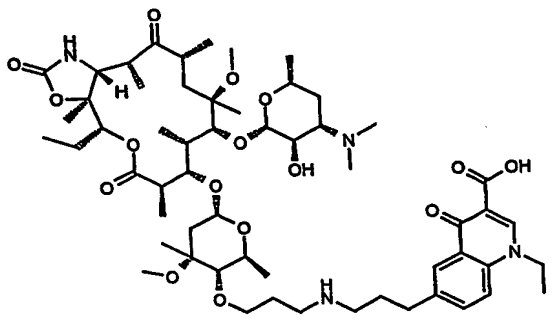
f) 4"-*O*-(3-Oxopropyl)-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate.

To **Example 7e** (0.082 g, 0.097 mmol) in DCM (3 mL) was added Dess-Martin periodinane (0.047 g, 0.11 mmol). The reaction was stirred for 1.75 h, then more oxidant (0.018 g) added. After a further 1.5 h, the reaction was diluted with DCM, washed with aq sodium hydrogen carbonate, dried and evaporated to give the crude title compound as a white foam (0.086 g), which was used without purification; ESMS *m/z* 843 $[M+H]^+$.

g) 4"-*O*-{3-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-propylamino]-propyl}-6-*O*-methyl-11-desoxy-11-(R)-methylamino-erythromycin A 11,12-carbamate formate.

Example 7f (0.082 g, 0.097 mmol) in methanol / DCM (1:1, 4 mL) was added to sodium acetate (0.0164 g, 0.2 mmol), acetic acid (0.2 mL), **Intermediate 4** (0.0274 g, 0.1 mmol), and 3A molecular sieves (0.2 g). The mixture was stirred for 20 min then a solution of sodium cyanoborohydride (0.0126 g, 0.2 mmol) in methanol (0.3 mL) was added and stirring continued for 16 h. The reaction was then filtered, washing well with methanol and DCM, and the filtrate evaporated. The residue was purified by preparative reverse phase HPLC (MeCN/H2O/0.1%HCO2H eluent) to give the title compound as an off-white powder (0.038 g, 35%); ESMS *m/z* 1101 $[M+H]^+$.

Example 8: 4"-*O*-{3-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-propylamino]-propyl}-6-*O*-methyl-11-desoxy-11-(R)-amino-erythromycin A 11,12-carbamate formate



a) 2'-*O*,3'-*N*-bis(Benzyloxycarbonyl)-3'-*N*-desmethyl-4"-*O*-[3-(*tert*-butyldimethylsilyl-oxy)propyl]-6-*O*-methyl-erythromycin A 11,12-carbonate.

Example 2a (1.85 g, 1.71 mmol) in DMF (10 mL) was treated sequentially with imidazole (0.128 g, 1.88 mmol) and tert-butyldimethylsilyl chloride (0.283 g, 1.88 mmol). Mixture stirred for 20 h then evaporated. Water was added and the mixture extracted with diethyl ether. The combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography on silica gel (100 g), eluting with 12-42% ethyl acetate in petroleum ether, to give the title compound as a white foam (1.923 g); ESMS *m/z* 1217 $[M+NH_4]^+$.

b) 2'-O,3'-*N*-bis(Benzyloxycarbonyl)-3'-*N*-desmethyl-4"-*O*-[3-(tert-butyldimethylsilyl-oxy)propyl]-6-*O*-methyl-11-desoxy-11-(R)-amino-erythromycin A 11,12-carbamate.

Example 8a (1.9 g, 1.58 mmol), carbonyldiimidazole (1.28 g, 7.2 mmol), imidazole (0.01 g) and DBU (0.08 g, 0.52 mmol) were dissolved in THF (10 mL), heated to 40°C and stirred for 17 h. Further portions of carbonyldiimidazole and DBU were added, and reaction heated at 60°C for 6 h then 50°C for 16 h. The mixture was then cooled in an ice bath and ammonia gas bubbled in for 8 h. The reaction was then stored in the fridge for 14 h. Argon was then bubbled through the mixture before the addition of potassium tert-butoxide (1 M in THF, 1.74 mL, 1.74 mmol). After 5 h at room temperature more potassium tert-butoxide (1 M in THF, 1 mL, 1 mmol) was added. Further 2 h then more potassium tert-butoxide (1 M in THF, 0.5 mL, 0.5 mmol) added. The mixture was then stirred for 64 h. Aqueous sodium hydrogen carbonate was then added and the mixture extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography on silica gel (100 g), eluting with 20-52% ethyl acetate in petroleum ether, to give the title compound as a white foam (1.3 g); ESMS *m/z* 1216 $[M+NH_4]^+$.

c) 4"-*O*-[3-(tert-butyldimethylsilyl-oxy)propyl]-6-*O*-methyl-11-desoxy-11-(R)-amino-erythromycin A 11,12-carbamate.

Example 8b (1.4 g, 1.17 mmol) was disolved in methanol (10 mL) and 1,4-dioxane (15 mL), and hydrogenated over 10% palladium on charcoal (50% aq paste, 0.4 g) for 6h. Formaldehyde (37% aq, 4 ml), pH 4.5 acetate buffer (4 mL) and more catalyst (0.2 g) were then added, and the mixture hydrogenated for 24 h. The mixture was then filtered,

washing well with methanol and 1,4-dioxane. The filtrate was evaporated, and the residue purified by chromatography on silica gel (100 g). Elution with 0-7% '2 M NH_3 in methanol' in dichloromethane, gave the title compound as a white foam (0.969 g); ESMS *m/z* 945 $[M+H]^+$.

d) 4"-*O*-(3-Hydroxypropyl)-6-*O*-methyl-11-desoxy-11-(R)-aminoerythromycin A 11,12-carbamate.

Example 8c (0.17 g, 0.18 mmol) in THF (4 mL) and acetic acid (0.023 mL, 0.4 mmol) was treated with tetrabutylammonium fluoride (1 M in THF, 0.4 mL, 0.4 mmol). The mixture was stirred at 35°C for 72 h, then evaporated to dryness, and the residue purified by chromatography on silica gel (40 g). Elution with 0-11% '2 M NH_3 in methanol' in dichloromethane, gave the title compound as a white foam (0.15 g); ESMS *m/z* 831 $[M+H]^+$.

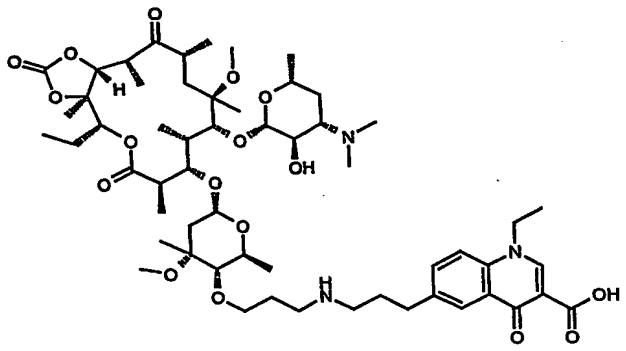
e) 4"-*O*-(3-Oxopropyl)-6-*O*-methyl-11-desoxy-11-(R)-aminoerythromycin A 11,12-carbamate.

To **Example 8d** (0.085 g, 0.1 mmol) in DCM (2 mL) was added Dess-Martin periodinane (0.051 g, 0.12 mmol) in DCM (1 mL). Stirred for 1.3 h, then diluted with DCM, washed with aq sodium hydrogen carbonate, dried and evaporated to give the crude title compound as a white foam (0.097 g), which was used without purification; ESMS *m/z* 829 $[M+H]^+$.

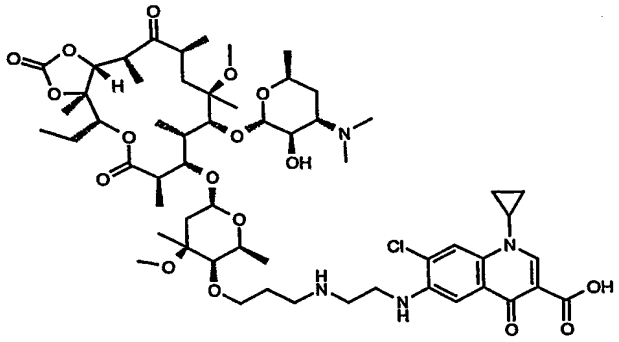
f) 4"-*O*-{3-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)-propylamino]-propyl}-6-*O*-methyl-11-desoxy-11-(R)-amino-erythromycin A 11,12-carbamate formate.

Example 8d (0.082 g, 0.1 mmol) in methanol / DCM (1:1, 4 mL) was added to sodium acetate (0.025 g, 0.3 mmol), acetic acid (0.2 mL), **Intermediate 4** (0.043 g, 0.11 mmol), and 3A molecular sieves (0.2 g). The mixture was stirred for 30 min then a solution of sodium cyanoborohydride (0.0126 g, 0.2 mmol) in methanol (0.3 mL) was added and stirring continued for 2.5 h. The reaction was then filtered, washing well with methanol and DCM, and the fitrate evaporated. The residue was purified by preparative reverse phase HPLC (MeCN/H_2O/0.1%HCO_2H eluent) to give the title compound as a pale yellow solid (0.054 g, 46%); ESMS *m/z* 1087 $[M+H]^+$.

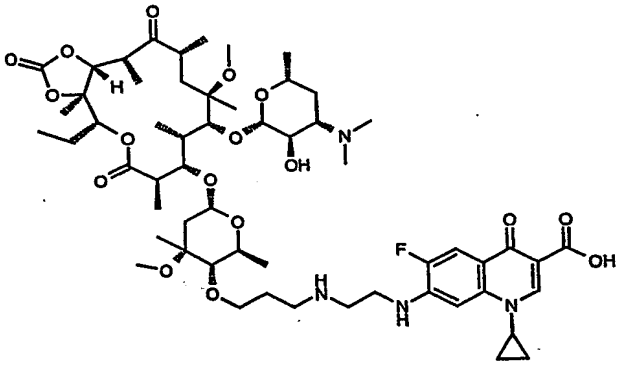
Example 9: 4"-*O*-{3-[3-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)propylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate formate



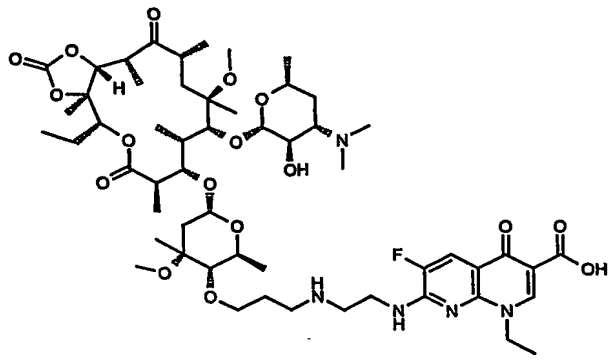
Example 10: 4"-*O*-{3-[2-(3-Carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate formate



Example 11: 4"-*O*-{3-[2-(3-Carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate formate



Example 12: 4"-*O*-{3-[2-(3-Carboxy-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridin-7-ylamino)ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate formate



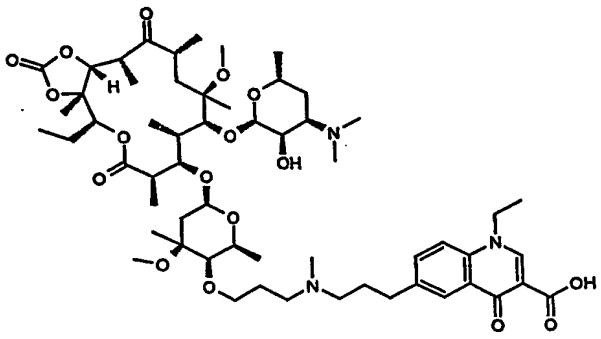
To 4"-O-(3-hydroxypropyl)-6-O-methylerythromycin A 11,12-carbonate (0.883 g, 1.06 mmol) in dichloromethane (20 mL) under argon was added Dess-Martin periodinane (0.495 g, 1.17 mmol). After 3 h, more Dess-Martin periodinane (0.1 g, 0.24 mmol) was added, and after 1.5 h more Dess-Martin periodinane (0.11 g, 0.26 mmol) was added. The mixture was stirred for a further 35 min then diluted with dichloromethane, washed with saturated aqueous sodium hydrogen carbonate, dried, filtered, and concentrated *in vacuo* to give the crude aldehyde as a white solid foam. This material was dissolved in methanol (20 mL) and dichloromethane (20 mL), then split into four equal portions which were used in the general procedure for reductive amination.

General Procedure for Reductive Amination

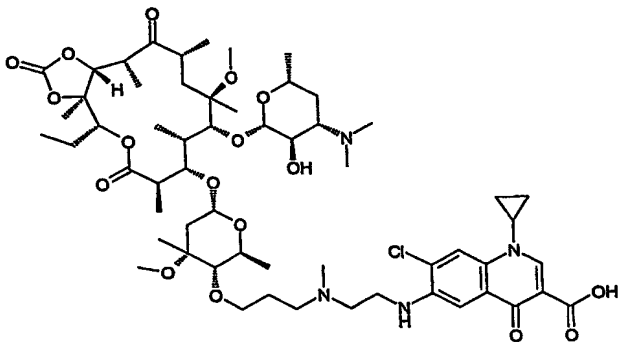
To the solution of aldehyde in methanol (5 mL) and dichloromethane (5 mL) was added sodium acetate (0.044 g, 0.54 mmol), acetic acid (0.5 mL), 3A molecular sieves (0.5 g), and the amine (0.26 mmol). The mixture was stirred for 10 min then a solution of sodium cyanoborohydride (0.033 g, 0.5 mmol) in methanol (0.5 mL) was added and stirring continued for 20 h. The reaction was then filtered through Celite, and concentrated *in vacuo* to give a residue which was purified by preparative reverse phase HPLC (MeCN/H_2O/0.1%HCO_2H eluent), then further purified by chromatography (silica gel, 0-20% 2 M methanolic ammonia in dichloromethane) to give the title compound.

Amine intermediate	Example no.	Mass (g)	ESMS *m/z* $[M+H]^+$
4	**9**	0.096	1088
1	**10**	0.111	1135
7-(2-aminoethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	**11**	0.103	1119
6	**12**	0.084	1108

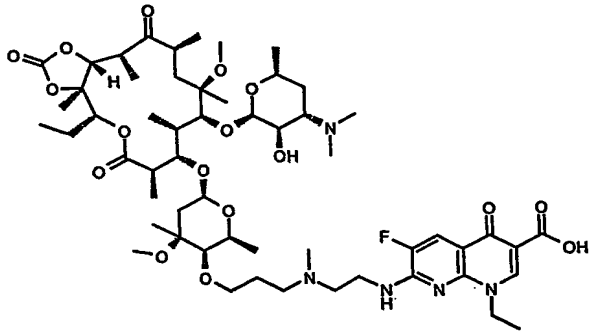
Example 13: 4"-*O*-(3-{[3-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)propyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate formate



Example 14: 4"-*O*-(3-{[2-(3-Carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)ethyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate



Example 15: 4"-*O*-(3-{[2-(3-Carboxy-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridin-7-ylamino)ethyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate



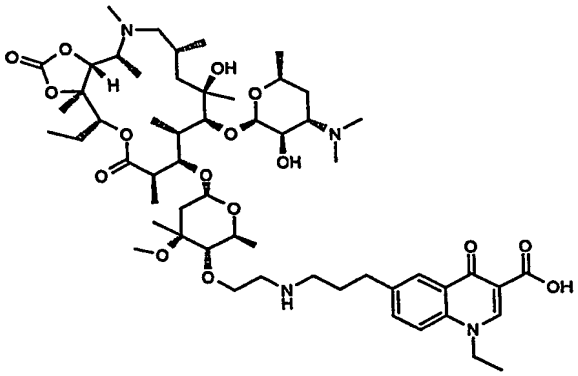
General Procedure for *N*-Methylation

To a solution of amine starting material (0.072 mmol) in chloroform (2 mL) was added formic acid (0.005 mL, 0.144 mmol), and formaldehyde (37% by weight in water) (0.011 mL, 0.144 mmol). The mixture was heated to 60°C for 3 h then concentrated *in vacuo* to give a residue which was purified by chromatography (silica gel, 0-20% 2 M methanolic

ammonia in dichloromethane) or by preparative reverse phase HPLC (MeCN/H_2O/0.1%HCO_2H eluent) to give the title compound.

Starting material	Product example no.	ESMS *m/z* $[M+H]^+$
Example 9	13	1102
Example 10	14	1149
Example 12	15	1122

Example 16: 4"-*O*-{2-[3-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)propylamino]ethyl}azithromycin 11,12-carbonate



a) 2'-*O*-Acetyl-azithromycin 11,12-carbonate.
To a suspension of azithromycin 11,12-carbonate (B.A. Jones et al., *Tet. Lett.*, 1993, *34*, 4913; 100 g, 0.13 mol) and sodium hydrogen carbonate (44 g, 0.52 mol) in dichloromethane (400 mL) was added dropwise acetic anhydride (20.4 mL, 0.2 mol). After stirring overnight the mixture was diluted with water (400 mL) and the organic layer separated, dried and evaporated to yield the title compound as a white solid; ESMS *m/z* 818 (MH^+).

b) 2'-*O*-Acetyl-4"-*O*-allyl-azithromycin 11,12-carbonate.
To a solution of **Example 16a** (0.408 g, 0.5 mmol) in dry THF (4 mL) and tetrakis(triphenyphosphine) palladium (0.057 mg, 0.05 mmol) was added allyl *t*-butyl carbonate (0.300 g, 1.89 mmol). After heating at reflux under argon for 8 h the mixture was cooled and the solvent evaporated. Chromatography of the residue over silica gel eluting with dichloromethane containing an increasing concentration of methanol (0–1%) gave the title compound as a pale yellow gum; ESMS *m/z* 857 (MH^+).

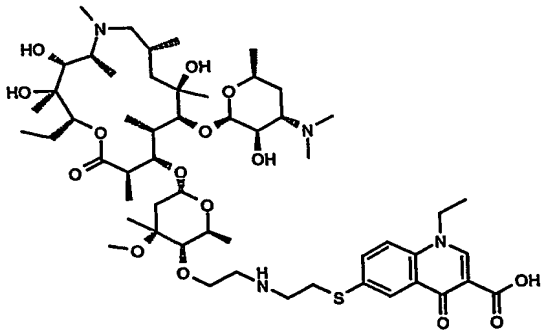
c) 2'-*O*-Acetyl-4"-*O*-(2-oxoethoxy)azithromycin 11,12-carbonate.
To a cooled solution of **Example 16b** (0.20 g, 0.23 mmol) in THF (1 mL) and water (1 mL) was added osmium tetraoxide (15 µL of a 4% solution in water). After 5 mins solid sodium periodate (0.21 g, 1 mmol) was added in one portion and the resultant mixture stirred at

room temperature for 4 h. Sodium hydrogen sulfite (0.19 g, 1 mmol) was added and the organic material extracted with ethyl acetate (2 x 15 mL). The combined organic fractions were dried and evaporated to yield the title compound as a brown gum; ESMS *m/z* 877 (MNH_4^+).

d) 4"-*O*-{2-[3-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)propylamino]ethyl} azithromycin 11,12-carbonate.

A solution of **Example 16c** (0.054 g, 0.063 mmol), **Intermediate 4** (0.05 g, 0.127 mmol) and sodium acetate (0.011 g, 0.127 mmol) in 1% acetic acid/methanol (2 mL) was stirred for 0.5 h at room temperature. Sodium cyanoborohydride (0.016 mg, 0.25 mmol) was added. After 16 h the mixture was concentrated and purified by reverse phase liquid chromatography to yield the title compound as a white solid; ESMS *m/z* 1076 (MH^+).

Example 17: 4"-*O*-{2-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-ylsulfanyl)ethylamino]ethyl}azithromycin tris trifluoroacetate



a) 2'-*O*-Acetyl-4"-*O*-{2-[2-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-ylsulfanyl)ethylamino]ethyl}azithromycin 11,12-carbonate.

Using a similar procedure to that described in **Example 16d**, **Example 16c** (0.055 g, 0.063 mmol) and **Intermediate 3** (0.030 g, 0.95 mmol) gave the title compound as a white solid; ESMS *m/z* 1136 (MH^+).

b) 4"-*O*-{2-[2-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-ylsulfanyl)ethylamino]ethyl}azithromycin tris trifluoroacetate.

A solution of **Example 17a** in methanol (2 mL) containing sodium hydrogen carbonate (0.010g, 0.12 mmol) was stirred at 50°C. After 4 h the mixture was cooled, filtered and the solvent evaporated to yield the crude product. Purification by reverse phase liquid chromatography gave the title compound as a colourless gum; ESMS *m/z* 1094 (MH^+).

Biological Data

The MIC (μg/ml) of test compounds against various organisms was determined including:

S. aureus Smith ATCC 13709, *S. pneumoniae* SP030, *S. pyogenes* 3565, *E. faecalis* ATCC 29212, *H. influenzae* ATCC 49247, *M. catarrhalis* ATCC 23246.

Examples 1, 2, 5-7, 13 and 15 have an MIC $\leq$1 μg/ml against *S. aureus* Smith ATCC 13709, *S. pneumoniae* SP030, *S. pyogenes* 3565 and *E. faecalis* ATCC 29212.

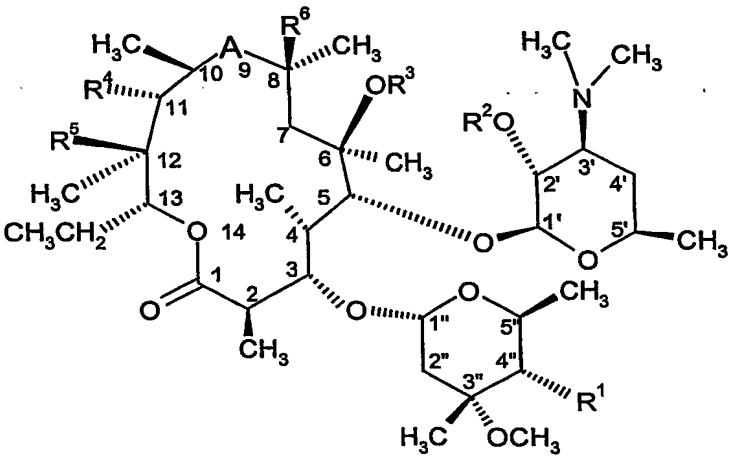
Examples 1,2, 4, 6 and 13-16 have an MIC $\leq$4 μg/ml against *H. influenzae* ATCC 49247 and *M. catarrhalis* ATCC 23246.

Examples 1-4, 6, 7 and 9-15 have an MIC $\leq$1 μg/ml against erythromycin resistant strains of *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A compound of formula (I)



(I)

wherein

A is a bivalent radical selected from -C(O)-, -C(O)NH-, -NHC(O)-, -N(R^7)-CH_2-, -CH_2-N(R^7)-, -CH(NR^8R^9)- and -C(=NR^{10})-;

R^1 is -O(CH_2)$_d$XR^{11};

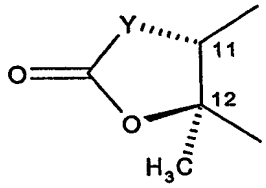
R^2 is hydrogen or a hydroxyl protecting group;

R^3 is hydrogen, C_{1-4}alkyl, or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R^4 is hydroxy, C_{3-6}alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl, or C_{1-6}alkoxy optionally substituted by C_{1-6}alkoxy or -O(CH_2)$_e$$NR^7R^{12}$,

R^5 is hydroxy, or

R^4 and R^5 taken together with the intervening atoms form a cyclic group having the following structure:



wherein Y is a bivalent radical selected from -CH_2-, -CH(CN)-, -O-, -N(R^{13})- and -CH(SR^{13})-;

R^6 is hydrogen or fluorine;

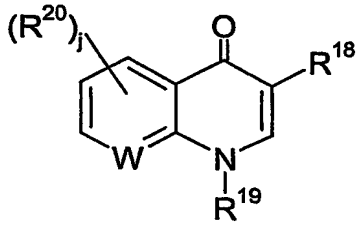
R^7 is hydrogen or C_{1-6}alkyl;

R^8 and R^9 are each independently hydrogen, C_{1-6}alkyl, -C(=NR^{10})$NR^{14}R^{15}$ or -C(O)R^{14}, or

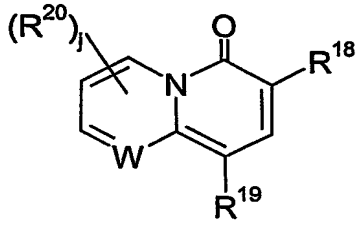
R^8 and R^9 together form $=CH(CR^{14}R^{15})_f$aryl, $=CH(CR^{14}R^{15})_f$heterocyclyl, $=CR^{14}R^{15}$ or $=C(R^{14})C(O)OR^{14}$, wherein the alkyl, aryl and heterocyclyl groups are optionally substituted by up to three groups independently selected from R^{16};

R^{10} is $-OR^{17}$, C_{1-6}alkyl, $-(CH_2)_g$aryl, $-(CH_2)_g$heterocyclyl or $-(CH_2)_hO(CH_2)_iOR^7$, wherein each R^{10} group is optionally substituted by up to three groups independently selected from R^{16};

R^{11} is a heterocyclic group having the following structure:



or



R^{12} is hydrogen or C_{1-6}alkyl;

R^{13} is hydrogen or C_{1-4}alkyl substituted by a group selected from optionally substituted phenyl, optionally substituted 5 or 6 membered heteroaryl and optionally substituted 9 to 10 membered fused bicyclic heteroaryl;

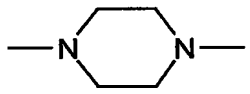
R^{14} and R^{15} are each independently hydrogen or C_{1-6}alkyl;

R^{16} is halogen, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{21}$, $-C(O)OR^{21}$, $-OC(O)R^{21}$, $-OC(O)OR^{21}$, $-NR^{22}C(O)R^{23}$, $-C(O)NR^{22}R^{23}$, $-NR^{22}R^{23}$, hydroxy, C_{1-6}alkyl, $-S(O)_kC_{1-6}$alkyl, C_{1-6}alkoxy, $-(CH_2)_m$aryl or $-(CH_2)_m$heteroaryl, wherein the alkoxy group is optionally substituted by up to three groups independently selected from $-NR^{14}R^{15}$, halogen and $-OR^{14}$, and the aryl and heteroaryl groups are optionally substituted by up to five groups independently selected from halogen, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{24}$, $-C(O)OR^{24}$, $-OC(O)OR^{24}$, $-NR^{25}C(O)R^{26}$, $-C(O)NR^{25}R^{26}$, $-NR^{25}R^{26}$, hydroxy, C_{1-6}alkyl and C_{1-6}alkoxy;

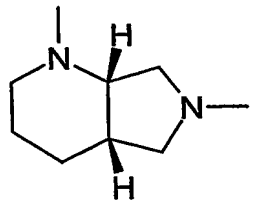
R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl or a 5 or 6 membered heterocyclic group, wherein the alkyl, cycloalkyl, alkenyl and heterocyclic groups are optionally substituted by up to three substituents independently selected from optionally substituted 5 or 6 membered heterocyclic group, optionally substituted 5 or 6 membered heteroaryl, $-OR^{27}$, $-S(O)_nR^{27}$, $-NR^{27}R^{28}$, $-CONR^{27}R^{28}$, halogen and cyano;

R^{18} is hydrogen, $-C(O)OR^{29}$, $-C(O)NHR^{29}$ or $-C(O)CH_2NO_2$;

R^{19} is hydrogen, C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy, C_{3-7}cycloalkyl, or optionally substituted phenyl or benzyl;
R^{20} is halogen, C_{1-4}alkyl, C_{1-4}thioalkyl, C_{1-4}alkoxy, $-NH_2$, $-NH(C_{1-4}alkyl)$ or $-N(C_{1-4}alkyl)_2$;
R^{21} is hydrogen, C_{1-10}alkyl, $-(CH_2)_p$aryl or $-(CH_2)_p$heteroaryl;
R^{22} and R^{23} are each independently hydrogen, $-OR^{14}$, C_{1-6}alkyl, $-(CH_2)_q$aryl or $-(CH_2)_q$heterocyclyl;
R^{24} is hydrogen, C_{1-10}alkyl, $-(CH_2)_r$aryl or $-(CH_2)_r$heteroaryl;
R^{25} and R^{26} are each independently hydrogen, $-OR^{14}$, C_{1-6}alkyl, $-(CH_2)_s$aryl or $-(CH_2)_s$heterocyclyl;
R^{27} and R^{28} are each independently hydrogen, C_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl;
R^{29} is hydrogen or C_{1-6}alkyl optionally substituted by up to three groups independently selected from halogen, C_{1-4}alkoxy, $-OC(O)C_{1-6}$alkyl and $-OC(O)OC_{1-6}$alkyl;
R^{30} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, optionally substituted phenyl or benzyl, acetyl or benzoyl;
R^{31} is hydrogen or R^{20}, or R^{31} and R^{19} are linked to form the bivalent radical $-O(CH_2)_2-$ or $-(CH_2)_t-$;
X is $-U(CH_2)_vB-$, $-U(CH_2)_v-$ or a group selected from:



and



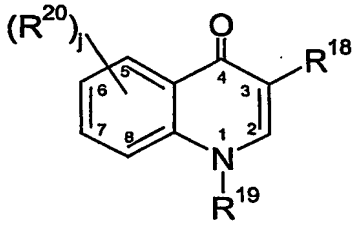
U and B are independently a divalent radical selected from $-N(R^{30})-$, $-O-$, $-S(O)_z-$, $-N(R^{30})C(O)-$, $-C(O)N(R^{30})-$ and $-N[C(O)R^{30}]-$;
W is $-C(R^{31})-$ or a nitrogen atom;
d is an integer from 2 to 6;
e is an integer from 2 to 4;
f, g, h, m, p, q, r and s are each independently integers from 0 to 4;
i is an integer from 1 to 6;
j, k, n and z are each independently integers from 0 to 2;
t is 2 or 3;
v is an integer from 2 to 8;
or a pharmaceutically acceptable derivative thereof.

2. A compound according to claim 1 wherein A is $-C(O)-$ or $-N(R^7)-CH_2-$.

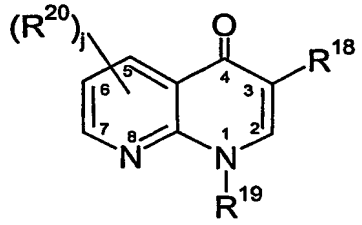
3. A compound according to claim 1 or claim 2 wherein X is $-U(CH_2)_vB-$ or $-U(CH_2)_v$.

4. A compound according to any one of the preceding claims wherein d is 2 or 3.

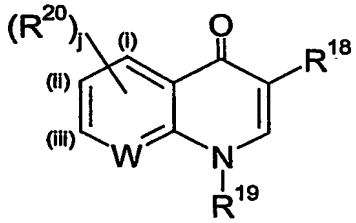
5. A compound according to any one of the preceding claims wherein R^{11} is a heterocyclic group of the following formula:



or



wherein the heterocyclic is linked in the 6 or 7 position and j, R^{18}, R^{19} and R^{20} are as defined in claim 1, or a heterocyclic group of the following formula:



wherein the heterocyclic is linked in the (ii) or (iii) position, W is $-C(R^{31})-$ and R^{31} and R^{19} are linked to form the bivalent radical $-(CH_2)_t-$ as defined in claim 1, and j, R^{18}, R^{19} and R^{20} are as defined in claim 1.

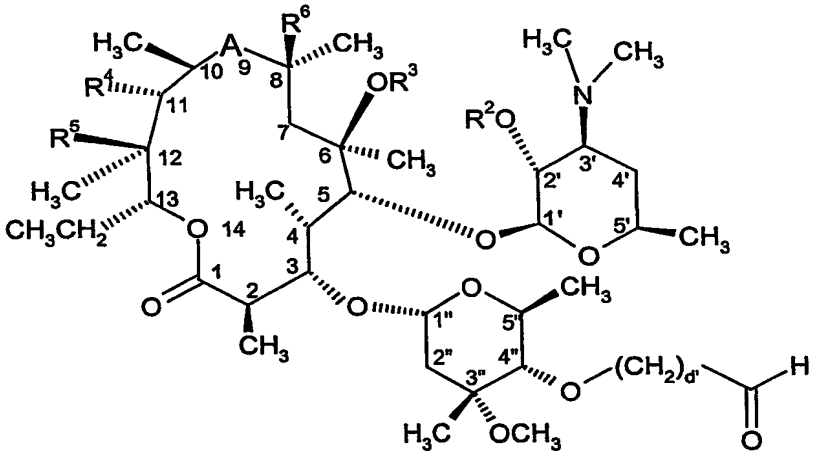
6. A compound according to claim 1 as defined in any one of Examples 1 to 17, or a pharmaceutically acceptable derivative thereof.

7. A compound selected from:

4"-*O*-(2-{[2-(3-carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethyl]-methylamino}-ethyl)-6-*O*-methyl-erythromycin A 11,12-carbonate;
4"-*O*-(3-{[2-(3-carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinolin-7-ylamino)ethyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate;
4"-*O*-{3-[2-(2-carboxy-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-9-yloxy)-ethylamino]-propyl}-6-*O*-methyl-erythromycin A 11,12-carbonate;
4"-*O*-(3-{[3-(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-quinolin-6-yl)propyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate; and
4"-*O*-(3-{[2-(3-carboxy-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridin-7-ylamino)ethyl]-methylamino}-propyl)-6-*O*-methyl-erythromycin A 11,12-carbonate;
or a pharmaceutically acceptable derivative thereof.

8. A process for the preparation of a compound as claimed in claim 1 which comprises:

a) reacting a compound of formula (II)

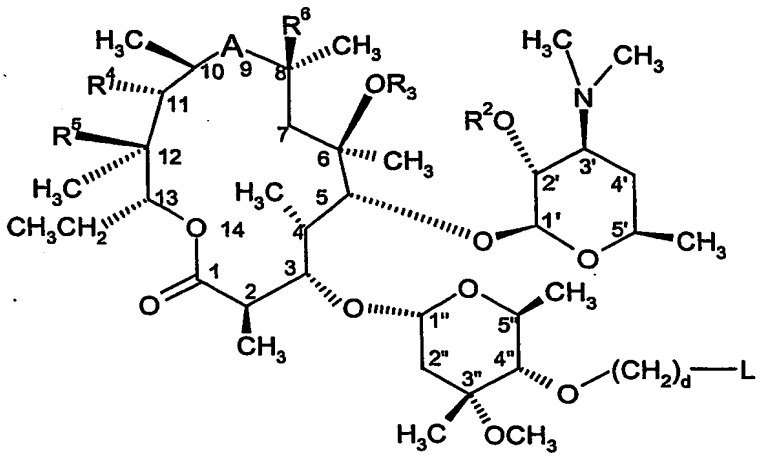


(II)

$HN(R^{30})(CH_2)_vB^aR^{11a}$ (IIIa) $HN(R^{30})(CH_2)_vR^{11a}$ (IIIb)

with a suitable amine (IIIa) or (IIIb), wherein B^a and R^{11a} are B and R^{11} as defined in claim 1 or groups convertible to B and R^{11}; or

b) reacting a compound of formula (V)



(V)

with a compound of formula X^aR^{11a} (IV), wherein R^{11a} is R^{11} as defined in claim 1 or a group convertible to R^{11} and X^a is $-U(CH_2)_V-$ or $-U(CH_2)_VB-$, or a group convertible to $-U(CH_2)_V-$ or $-U(CH_2)_VB-$, in which U is a group selected from $-N(R^{30})-$ and -S-, and L is suitable leaving group, to produce a compound of formula (I) wherein U is a group selected from $-N(R^{30})-$ and -S-, and thereafter, if required, subjecting the resulting compound to one or more of the following operations:

i) removal of the protecting group R^2,

ii) conversion of X^aR^{11a} to XR^{11},

iii) conversion of B^aR^{11a} to R^{11},

iv) conversion of R^{11a} to R^{11},

and

v) conversion of the resultant compound of formula (I) into a pharmaceutically acceptable derivative thereof.

9. A compound as claimed in any one of claims 1 to 7 for use in therapy.

10. The use of a compound as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in the treatment or prophylaxis of systemic or topical microbial infections in a human or animal body.

11. The use of a compound as claimed in any one of claims 1 to 7 for use in the treatment or prophylaxis of systemic or topical microbial infections in a human or animal body.

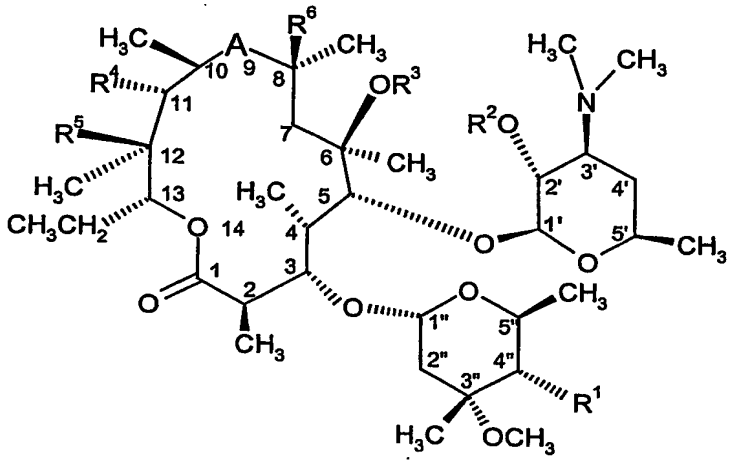
12. A method for the treatment of the human or non-human animal body to combat microbial infection comprising administration to a body in need of such treatment of an effective amount of a compound as claimed in any one of claims 1 to 7.

13. A pharmaceutical composition comprising at least one compound as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable excipient, diluent and/or carrier.

ABSTRACT

NOVEL COMPOUNDS

The present invention relates to 14- or 15-membered macrolides substituted at the 4" position of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, to processes for their preparation and their use in therapy or prophylaxis of systemic or topical microbial infections in a human or animal body.